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Description

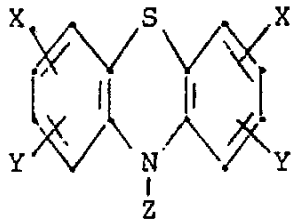
Phenothiazine derivatives and analogs thereof are useful as inhibitors of the biosynthesis of mammalian leukotrienes. As such, these compounds are useful therapeutic agents for treating allergic conditions, asthma, cardiovascular disorders, inflammation and certain skin diseases.

The leukotrienes are a novel group of biologically active substances derived from arachidonic acid through the action of the 5-lipoxygenase enzyme system. There are two groups of leukotrienes derived from a common unstable precursor Leukotriene A_4. The first of these are the peptido-lipid leukotrienes, the most important being Leukotrienes C_4 and D_4. These compounds collectively account for the biologically active material known as the slow reacting substance of anaphylaxis.

The leukotrienes are potent smooth muscle contracting agents, particularly on respiratory smooth muscle but also on other tissues (e.g., gall bladder). In addition, they promote mucous production, modulate vascular permeability changes and are potent inflammatory agents in human skin. The most important compound in the second group of leukotrienes is Leukotriene B_4, a dihydroxy fatty acid. This compound is a potent chemotactic agent for neutrophils and eosinophils. It also effects other cell types such as lymphocytes and for example may modulate the action of T-suppressor cells and natural killer cells. When injected in vivo, in addition to promoting the accumulation of leukocytes, Leukotriene B_4 is also a potent hyperalgesic agent and can modulate vascular permeability changes through a neutrophil dependent mechanism. See: D. M. Bailey and F. B. Casey, Ann. Rpts. Med. Chem. 17, 203 (1982).

As indicated above, the leukotrienes have been implicated in numerous disease states. Inhibition of leukotriene biosynthesis and/or antagonism of leukotriene action, will therefore provide a therapeutic benefit to patients suffering from leukotriene mediated disease states. These disease states include, but are not limited to; asthma; allergic conditions such as allergic rhinitis; skin diseases including psoriasis and atopic dermatitis; inflammation; gouty arthritis; gall bladder spasms; and cardiovascular disorders such as angina.

Phenothiazine derivatives of the general Formula II are known compounds:



II

See for example; "Progress in Drug Research", Volume 5, E. Tucker, ed., Birkhauser Verlag, Basel Switzerland (1963) pages 274-383; V. A. Rigas et al., Prostaglandins Med. 183 (1981); J. M. Perel et al., Neurotoxicology, Raven Press, New York, 1977, pp. 9-13; V. Fishman et al., J. Pharm. Exp. Ther. 150 165 (1965); Arch. Intern. Pharm. Ther. 74 314 (1947); N. Bhargava et al., Gazz. Chim. Ital. 109 201 (1979); V. F. Garry et al., Biochem. Pharm. 21 2801 (1972); S. C. Mitchell et al., Drug Met. Disp. 7 399 (1979); T. Akera et al., Biochem. Pharm. 27 995 (1978); I. Creese et al., Europ. J. Pharm., 47 291 (1978); S. C. Mitchell, Drug Met. Rev., 13 319 (1982); T. Ellison et al., Am. J. Vet. Res. (7) 519 (1957); K. P. Singh et al., Asian Med. J. 19 296 (1976) and H. B. Collier, Can. J. Med. Sci. 31 195 (1953).

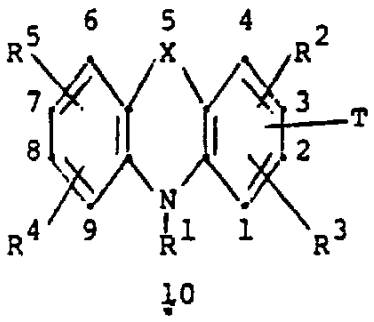
Several derivatives of phenothiazine are known to be inhibitors of enzymes, including the 15-lipoxygenase enzyme isolated from soybeans. However, none of the compounds of Formula A are taught to have leukotriene biosynthesis inhibiting ability via the inhibition of the mammalian 5-lipoxygenase enzyme system.

It has been discovered that compounds of the Formula II type and analogs thereof are effective inhibitors of mammalian leukotriene biosynthesis and are thus useful in the treatment of conditions such as asthma, allergies, inflammation, psoriasis, and the like in mammals, especially in humans.

Compounds of the Formula II type and analogues thereof may also be used to treat or prevent mammalian (especially human) disease states such as erosive gastritis; erosive oesophagitis; inflammatory bowel disease; ethanol-induced haemorrhagic erosions; hepatic ischemia; noxious-agent-induced damage or necrosis of hepatic, pancreatic, renal, or myocardial tissue; liver parenchymal damage caused by hepatoxic agents such as CCl_4 and D-galactosamine; ischemic renal failure; disease-induced hepatic damage; bile-salt-induced pancreatic or gastric damage; trauma- or stress-induced cell damage; and glycerol-induced

renal failure.

The present invention provides pharmaceutical compositions containing a compound of the general Formula I or a pharmaceutically acceptable salt of such a compound, together with a pharmaceutically acceptable carrier, where Formula I is:



I

in which

X is Se,S,SO,SO_2 or O;

R^1 is H; C_{1-6} alkyl; acetyl; (C_{1-6} acyloxy)-(C_{1-6} alkyl); benzoyl; substituted benzoyl having C_{1-3} alkyl, halogen, CN, CF_3, $COOR^6$, CH_2COOR^6,$(CH_2)_nNR^8R^9$ (where n is 0, 1 or 2), C_{1-3} alkoxy, and/or OH substitution, (herein called "substituted as herein defined"); carbamoyl; $CO\text{-}NHR^7$; $COOR^7$; p-toluenesulfonyl; methanesulfonyl; an acyl group such that R^1-OH is an essential amino acid; benzyl; phenethyl; $(CH_2)_pOR^a$ where R^a is C_{1-6} alkyl or phenyl and p is an integer from 1 to 5 when R^a is phenyl and is an integer from 1 to 6 when R^a is alkyl; $(CH_2)_nCOOR^6$ where n is 0, 1 or 2; or (C_{1-6} acyloxy)-(C_{1-6} alkoxy) carbonyl;

each of R^2, R^3, R^4 and R^5, independently of the others, is hydrogen; C_{1-6} alkyl; C_{2-6} alkenyl or $-(CH_2)_qM$ where q is 0 or an integer from 1 to 6 and M is (a) $-OR^{15}$; (b) halogen; (c) $-CF_3$; (d) $-SR^{15}$; (e) phenyl or substituted phenyl as herein defined; (f) $COOR^6$; (g) $-CO\text{-}R^{14}$; (h) tetrazolyl; (i) $-NH\text{-}CO\text{-}R^7$; (j) $-NR^8R^9$; (k) $-NHSO_2R^{10}$ where R^{10} is OH, C_{1-6} alkyl, C_{1-6} alkoxy or phenyl; (l) $-CO\text{-}CH_2OH$; (m) $-SOR^{11}$ where R^{11} is C_{1-6} alkyl, phenyl, substituted phenyl as herein defined, $(CH_2)_mCOOR^6$ where m is an integer from 1 to 6, CN, formyl, or C_{1-4} perfluoroalkyl; (n) $-CONR^8R^9$; (o) $-SO_2NR^8R^9$; (p) $-SO_2R^{13}$ where R^{13} is hydrogen, OH, C_{1-6} alkyl, phenyl, substituted phenyl as herein defined, $(CH_2)_mCOOR^6$ where m is as defined above, CN, formyl, or C_{1-4} perfluoroalkyl; (q) $-NO_2$; (r) $-O\text{-}CO\text{-}R^{14}$; (s) $O\text{-}CO\text{-}NR^8R^9$; or (t) -CN;

each R^5, independently of the others, is hydrogen, C_{1-6} alkyl or phenyl;

each R^7, independently of the others, is C_{1-6} alkyl, benzyl, phenyl or (C_{1-6} acyloxy)-(C_{1-6} alkyl);

each R^8 and each R^9, independently of any others, is hydrogen, C_{1-4} acyl, phenyl, or substituted phenyl as herein defined; or an R^8 and an R^9 are joined through the N to which they are both attached to form a heterocycloalkyl group having from 5 to 8 ring atoms;

each R^{14}, independently of the others, is hydrogen, $(CH)_rCOOR^6$ where r is 0 or an integer from 1 to 4; C_{1-6} alkyl; C_{1-6} alkoxy; (C_{1-6} acyloxy)-(C_{1-6} alkoxy); phenyl; substituted phenyl as herein defined; or C_{1-6} aminoalkyl such that $R^{14}COOH$ is an essential amino acid;

each R^{15}, independently of any others, is hydrogen, (C_{1-5} alkoxy)-(C_{1-5} alkyl), C_{1-6} alkyl; benzyl; (C_{1-6} acyloxy)-(C_{1-6} alkyl); phenyl; substituted phenyl as herein defined; $-CH_2)_mCOOR^6$ where m is as defined above; CN; formyl; perfluoroalkyl; or $CH_2\text{-}R^{12}$ where R^{12} is C_{1-6} alkyl, dimethylamino or phenyl;

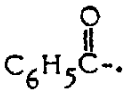
and T is hydrogen or $-OR_{15}$, where R_{15} is hydrogen, C_{1-6} alkyl, (C_{1-6} alkyl)-acyl, phenylacyl, substituted phenyl-acyl as herein defined; benzoyl; substituted benzoyl as herein defined; or arylsulfonyl; and compounds that are pharmaceutically acceptable salts thereof.

Certain compounds of Formula I and their pharmaceutically acceptable salts are novel.

The numbers surrounding Formula I designate the substituent positions, and R^2, R^3, R^4, R^5 and T may be positioned anywhere in the structure except at position 10.

The term alkyl, unless otherwise indicated, includes straight chain, branched chain and cycloalkyl groups of the number of carbon atoms shown. The term halogen, unless other indicated, include Cl, Br, I and F.

The C_{1-6} groups, such as C_{1-6} alkyl and C_{1-6} alkoxy, preferably contain 1 to 4 carbon atoms. The term phenylacyl means a group having the formula



The term aryl includes cyclic structures having the requisite degree of unsaturation to show a characteristic "aromatic" downfiled proton NMR spectrum. Examples include phenyl, substituted phenyl (as defined above in the definiation of R^{15}) naphthyl and anthracenyl, and include heteroaryl residues containing one or more O, N or S heteroatoms.

The term essential amino acid includes lysine, tryptophan, histidine, phenylalanine, leucine, isoleucine, threonine, methionine, valine, arginine, alanine, proline, glycine, serine, cysteine, tyrosine, asparagine, glutamine, aspartic acid and glutamic acid.

In those instances when asymetric centres are present, more than one stereoisomer is possible, and all possible isomeric forms are deemed to be included within the planar structural representations shown. Optically active (R) and (S) isomers may be resolved using conventional techniques.

In preferred compositions, X in Formula I is S, SO, SO_2 or O and the other variables are as described above.

In particularly preferred compounds in this group, R^2, R^3, R^4 and R^5 are all other than C_{2-6} alkenyl.

In a first especially preferred embodiment of the invention, the composition contains a compound of Formula I in which X is S or O;

R^1 is H; C_{1-6} alkyl; C_{1-6} acyl; (C_{1-6} acyloxy)-(C_{1-6} alkyl); (C_{1-6} alkoxy)-(C_{1-6} alkyl); benzoyl; benzoyl substituted as herein defined; carbamoyl; CO-NHR^7; COOR^7; $(CH_2)_pOR^a$ where R^a is C_{1-6} alkyl or phenyl, and p is an integer from 1 to 5; $(CH_2)_nCOOR^6$ where n is 0, 1 or 2; or (C_{1-6} acyloxy)-(C_{1-6} alkoxy) carbonyl;

M, if included in R^2, R^3, R^4 or R^5 is (a) -OR^{16}; (b) halogen; (c) $-CF_3$; (d) -SR^{16}; (e) COOR^5; (f) -NH-CO-R^7; (g) -NR^{8}R^9; (h) -SOR^{11} where R^{11} is C_{1-6} alkyl or C_{1-4} perfluoroalkyl; (i) $-SO_2R^{13}$ where R^{13} is C_{1-6} alkyl or C_{1-4} perfluoroalkyl; (j) -O-CO-R^{14} where R_{14} is H, C_{1-6} alkyl, phenyl or substituted phenyl as herein defined; (k) O-CO-NR^{8}R^9; or (1) -CN;

each R^{16}, independently of the others, is hydrogen; C_{1-6} alkyl; benzyl; (C_{1-6} acyloxy)(C_{1-6} alkyl) or C_{1-4} perfluoroalkyl;

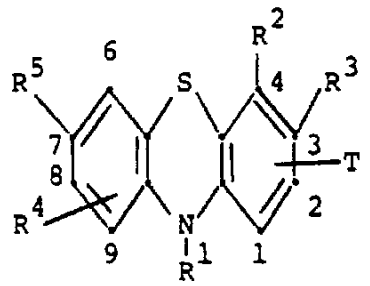
T is hydrogen or $-OR_{15}$, where R_{15} is hydrogen, C_{1-6} alkyl, (C_{1-6} alkyl)-acyl, phenylacyl, substituted phenyl-acyl as herein defined, benzoyl or substituted benzoyl as herein defined; and the other variables are as defined in the preceding paragraph.

In a second especially preferred embodiment of the invention, the composition contains a compound of Formula I in which X is O or S,

R^1 is hydrogen, C_{1-4} alkyl, C_{1-4} alkylacyl, $-(CH_2)_pOR^a$ where R^a is C_{1-4} alkyl or phenyl and p is 1, 2 or 3, (C_{1-4} acyloxy)-(C_{1-4} alkyl), (C_{1-4} alkoxy)carbonyl or (C_{1-6} acyloxy)-(C_{1-4} alkoxy)carbonyl;

each of R^2, R^3, R^4 and R^5, independently of the others, is hydrogen, halogen, hydroxyl; C_{1-3} alkyl; C_{1-3} alkoxy; C_{1-3} alkylthio; C_{1-5} acyloxy; benzoyloxy; C_{1-3} trihaloalkyl; C_{1-4} aminoalkyl; C_{1-5} acyl; $(CH_2)_mCOOR^6$, where m is 0, 1, 2, 3 or 4 and R^6 is H, phenyl or C_{1-6} alkyl; or (C_{1-4} acyloxy)-(C_{1-4} alkoxy)-carbonyl; and T is as defined above.

In a third especially preferred embodiment of the invention, the composition contains a compound of Formula III



III

in which

R^1 is H, C_{1-4} acyl, (C_{1-4} acyloxy)-(C_{1-4} alkyl), or C_{1-4} acyloxy)-(C_{1-4} alkoxy)carbonyl;

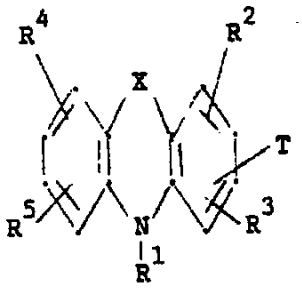
R^2 is halogen;

R^3 is OH, C_{1-5} acyloxy, benzoyloxy, or (C_{1-4} acyloxy)-(C_{1-4}alkoxy)carbonyloxy;
R^4 is H, OH, C_{1-4} alkoxy or C_{1-4} acyloxy and is located at either position 1 or position 2;
R^5 is OH, C_{1-4} alkoxy or C_{1-4} acyloxy;
T is hydrogen or C_{1-4} alkoxy.

In these preferred embodiments, a pharmaceutically acceptable salt may be used instead of the compound itself.

Examples of the Formula I compounds useful in the compositions of the present invention are tabulated below. In Table I, the number preceding the R^2-R^5 and T definitions signifies the groups position on the ring system. Standard abbreviations are used, for example, Ph for phenyl, Bz for benzoyl, Ts for p-toluenesulfonyl, Me for methyl, Bu for butyl, Et for ethyl and Ac for acetyl.

TABLE I



Compound[a]	X	R^1	R^2	R^3	R^4	R^5	T
1	S	H	H	H	H	H	H
2	S	Me	2-t-Bu	4-t-Bu	H	H	1-OH
3	S	Me	2-t-Bu	4-t-Bu	H	H	1-OMe
4	S	Me	2-t-Bu	4-t-Bu	H	H	1-OAc
5	S	Ac	2-t-Bu	4-t-Bu	H	H	1-OH
6	S	H	2-t-Bu	4-t-Bu	H	H	1-OMe
7	S	H	2-t-Bu	4-t-Bu	H	H	1-OAc
8	O	H	2-t-Bu	4-t-Bu	H	H	1-OH
9	S	CH_2OAc	2-t-Bu	4-t-Bu	H	H	1-OH
10	S	H	1-Cl	H	H	H	3-OH
11	S	H	1-Cl	H	H	H	3-OAc
12	S	H	1-Cl	H	H	H	3-OMe
13[1]	S	Me	1-Cl	H	H	H	3-OH
14[1]	S	Me	1-Cl	H	H	H	3-OAc
15	S	Me	1-Cl	H	H	H	3-OMe
16	S	CH_2OAc	1-Cl	H	H	H	3-OMe
17	S	CH_2OAc	1-Cl	H	H	H	3-OAc
18	O	H	1-Cl	H	H	H	3-OH

a The symbol 1 next to the number of a compound indicates which compounds are preferred and the symbol 2 next to the number of a compound indicates which compounds are also more preferred.

TABLE I (cont'd)

Compound	X	R^1	R^2	R^3	R^4	R^5	T
19	O	Me	1-Cl	H	H	H	3-OH
20	O	Me	1-Cl	H	H	H	3-OAc
21	O	Me	1-Cl	H	H	H	3-OMe
22	O	Ac	1-Cl	H	H	H	3-OAc
23	O	CH_2OAc	1-Cl	H	H	H	3-OMe
24	Se	Me	1-Cl	H	H	H	3-OMe
25	SO	H	1-Cl	H	H	H	3-OH
26	SO	H	1-Cl	H	H	H	3-OMe
27	SO	H	1-Cl	H	H	H	3-OAc
28	SO	Me	1-Cl	H	H	H	3-OH
29	SO	Me	1-Cl	H	H	H	3-OAc
30	SO	Me	1-Cl	H	H	H	3-OMe
31[1]	SO_2	H	1-Cl	H	H	H	3-OH
32	SO_2	H	1-Cl	H	H	H	3-OAc
33	SO_2	H	1-Cl	H	H	H	3-OMe
34	SO_2	Me	1-Cl	H	H	H	3-OAc
35	SO_2	Me	1-Cl	7-OCH_2CO_2H	H	H	3-OAc
36	SO_2	Me	1-Cl	H	H	H	3-OMe
37[1]	SO_2	Ac	1-Cl	H	H	H	3-OH
38[1]	SO_2	Ac	1-Cl	H	H	H	3-OAc
39	SO_2	Ac	1-Cl	H	H	H	3-OMe
40	SO	Ac	1-Cl	H	H	H	3-OH
41	SO	Ac	1-Cl	H	H	H	3-OAc
42	SO	Ac	1-Cl	H	H	H	3-OMe
43	SO_2	CH_2OAc	1-Cl	H	H	H	3-OH
44	SO_2	CH_2OAc	1-Cl	H	H	H	3-OAc
45	SO_2	CH_2OAc	1-Cl	H	H	H	3-OMe
46	S	CH_2Ph	H	H	H	H	H
47	S	Me	H	H	H	H	H

TABLE I (cont'd)

Compound	X	R^1	R^2	R^3	R^4	R^5	T
48	S	Ac	H	H	H	H	H
49	S	CH_2OAc	H	H	H	H	H
50	O	H	H	H	H	H	H
51	O	Me	H	H	H	H	H
52	O	Ac	H	H	H	H	H
53	Se	H	H	H	H	H	H
54	Se	Me	H	H	H	H	H
55	Se	Ac	H	H	H	H	H
56	Se	CH_2OAc	H	H	H	H	H
57	SO	H	H	H	H	H	H
58	SO	Me	H	H	H	H	H
59	SO_2	Ac	H	H	H	H	H
60	S	H	H	H	H	H	3-OH
61	S	H	H	H	H	H	3-OAc
62	S	H	H	H	H	H	3-OMe
63	S	Me	H	H	H	H	3-OAc
64	S	Me	H	H	H	H	3-OH
65	S	Me	H	H	H	H	3-OMe
66	S	Ac	H	H	H	H	2-OH
67	S	Ac	H	H	H	H	3-OAc
68	S	Ac	H	H	H	H	3-OMe
69	S	CH_2OAc	H	H	H	H	3-OH
70	S	CH_2OAc	H	H	H	H	3-OAc
71	S	CH_2OAc	H	H	H	H	3-OMe
72	Same as compounds 60-71 but X=O						
73[1]	Same as compounds 60-71 but X=Se						
74	S	H	4-Cl	H	H	H	3-OH
75	S	H	4-Cl	H	H	H	3-OMe
76[1]	S	H	4-Cl	H	H	H	3-OAc

TABLE I (cont'd)

Compound	X	R^1	R^2	R^3	R^4	R^5	T
77	S	Me	4-Cl	H	H	H	3-OH
78[1]	S	Me	4-Cl	H	H	H	3-OAc
79[1, 2]	S	Me	4-Cl	H	H	H	3-OMe
80[1, 2]	S	Ac	4-Cl	H	H	H	3-OH
81[1, 2]	S	Ac	4-Cl	H	H	H	3-OAc
82[1]	S	Ac	4-Cl	H	H	H	3-OMe
83	S	Me	4-Cl	H	H	H	3-O-Bz
84[1]	S	Me	4-Cl	H	H	H	3-OCOCH(Me)_2
85	S	Me	4-Cl	H	H	H	3-OCOC(Me)_3
86[1, 2]	SO_2	H	4-Cl	H	H	H	3-OH
87[1]	SO_2	H	4-OH	H	H	H	3-OH
88[1, 2]	SO_2	H	4-Cl	H	H	H	3-OAc
89	SO_2	H	4-Cl	H	H	H	3-OMe
90	SO_2	Me	4-Cl	H	H	H	3-OH
91	SO_2	Me	4-Cl	H	H	H	3-OAc
92[1]	SO_2	Me	4-Cl	H	H	H	3-OMe
93[1, 2]	SO_2	Ac	4-Cl	H	H	H	3-OH
94[1, 2]	SO_2	Ac	4-Cl	H	H	H	3-OAc
95	SO_2	Ac	4-Cl	H	H	H	3-OMe
96	S	CH_2OAc	4-Cl	H	H	H	H
97	S	CH_2OAc	4-Cl	H	H	H	3-OH
98	S	CH_2OAc	4-Cl	H	H	H	3-OAc
99	S	CH_2OAc	4-Cl	H	H	H	3-OMe
100	SO_2	CH_2OAc	4-Cl	H	H	H	3-OH
101	SO_2	CH_2OAc	4-Cl	H	H	H	3-OAc
102	SO_2	CH_2OAc	4-Cl	H	H	H	3-OMe
103	Same as compounds 74-103 but X=SO						
104	Same as compounds 74-103 but X=O						
105	Same as compounds 74-103 but R_4 is 7-Cl						

TABLE I (cont'd)

Compound	X	R^1	R^2	R^3	R^4	R^5	T
106	Same as compound 105 but X=O						
107	Same as compounds 74-103 but R_4 is 7-OMe						
108	Same as compound 107 but X=O						
109	Same as compounds 74-103 but R_4 is 7-(C_1-C_6 alkyl)						
110	Same as compound 109 but X=O						
111	Same as compounds 74-103 but R_4 is 7-(COMe)						
112	Same as compound 111 but X=O						
113	Same as compounds 74-103 but R_4 is 7-[$(CH_2)_m$COOR], wherein m is 0-4						
114	Same as compound 113 but X=O						
115	Same as compounds 74-103 but R_4 is 9-Cl						
116	S	H	4-Et	H	H	H	3-OH
117	S	Me	4-Et	H	H	H	3-$OCOCH_2Ph$
118	S	Me	4-Et	H	H	H	3-OAc
119	S	Me	4-Et	H	H	H	3-OMe
120	S	H	4-OEt	H	H	H	3-OH
121	S	H	4-OEt	H	H	H	3-OMe
122	S	Me	4-OEt	H	H	H	3-OMe
123	S	Me	4-OEt	H	H	H	3-OAc
124[1]	S	H	2-OEt	7-OEt	H	H	3-OH
125	S	H	2-OEt	7-OEt	H	H	3-OMe
126	S	Me	2-OEt	7-OEt	H	H	3-OMe
127	S	Me	2-OEt	7-OEt	H	H	3-OAc
128	S	H	H	H	H	H	3-OAC
129	S	Me	H	H	H	3-Ac	H
130	S	Ac	H	H	H	3-Ac	3-OAc
131	S	H	7-Ac	H	H	3-Ac	H
132	S	Me	7-Ac	H	H	3-Ac	H
133	S	Ac	7-Ac	H	H	3-Ac	H

TABLE I (cont'd)

Compound	X	R^1	R^2	R^3	R^4	R^5	T
134	S	CH_2OAc	7-Ac	H	H	3-Ac	H
135	S	H	2-Me	4-Cl	H	H	3-OH
136	S	Me	2-Me	4-Cl	H	H	3-OAc
137	S	H	7-Me	2-Me	H	H	3-OH
138	S	Me	7-Me	2-Me	H	H	3-OAc
139[1]	S	H	2-OEt	4-Cl	H	H	3-OH
140	S	Me	2-OEt	4-Cl	H	H	3-OAc
141	S	H	2-S-n-Bu	4-Cl	H	H	3-OH
142	S	Me	2-S-n-Bu	4-Cl	H	H	3-OAc
143	S	Me	4-S-n-Bu	H	H	H	3-OAc
144	S	Me	2-O-Me	4-Br	H	H	3-OAc
145	S	Me	2-O-Me	4-Cl	H	H	3-OAc
146	S	Me	2-O-Me	4-Br	H	H	3-OH
147[1]	S	H	2-O-Me	3-OH	H	H	7-OMe
148	S	H	1-OMe	3-OH	H	H	7-OMe
149	S	H	2-OMe	3-OH	1-Br	H	7-OMe
150	S	H	1-OMe	3-OH	2-Br	H	7-OMe
151[1]	S	H	1-OMe	3-OH	4-Br	H	7-OMe
152	S	H	1-OMe	3-OH	2-Cl	H	7-OMe
153[1]	S	H	1-OMe	3-OH	4-Cl	H	7-OMe
154	S	H	2-OMe	3-OH	1-Cl	H	7-OMe
155[1]	S	H	2-OMe	3-OH	4-Cl	H	7-OMe
156	S	H	2-OEt	3-OH	1-Br	H	7-OEt
157[1]	S	H	2-OEt	3-OH	4-Br	H	7-OEt
158	S	H	2-OEt	3-OH	1-Cl	H	7-OEt
159[1]	S	H	2-OEt	3-OH	4-Cl	H	7-OEt
160	S	H	2-OMe	3-OH	1-Br	7-OMe	9-OMe
161	S	H	2-OMe	3-OH	4-Br	7-OMe	8-OMe

TABLE I (cont'd)

Compound	X	R^1	R^2	R^3	R^4	R^5	T
162[1]	S	H	2-OMe	3-OH	4-F	H	7-OMe
163[1]	S	H	2-OMe	3-OH	4-CF_3	H	7-OMe
164[1]	S	H	2-OMe	3-OH	4-Br	H	7-OEt
165[1]	S	H	2-OMe	3-OH	4-Cl	H	7-OEt
166	S	H	2-OMe	3-OH	4-F	H	7-OEt
167	S	H	2-OMe	3-OH	4-I	H	7-OMe
168	S	H	2-OMe	3-OH	4-CF_3	H	7-OEt
169[1]	S	H	2-OEt	3-OH	4-Br	H	7-OMe
170[1]	S	H	2-OEt	3-OH	4-Cl	H	7-OMe
171	S	H	2-OEt	3-OH	4-F	H	7-OMe
172	S	H	2-OEt	3-OH	4-CF_3	H	7-OMe
173	S	H	1-OMe	2-OMe	3-OH	4-Br	7-OMe
174	S	H	1-OMe	3-OH	H	H	2-OMe
175	S	H	1-OMe	3-OH	4-Br	H	2-OMe
176	Same as compounds 147-175 but X=O						
177	Same as compounds 147-175 but X=SO_2						
178[1]	S	H	2-SMe	3-OH	4-Br	H	7-OMe
179[1]	S	H	2-OMe	3-OH	4-Br	7-SMe	H
180	SO_2	H	2-SO_2Me	3-OH	4-Br	H	7-OMe
181	Same as compounds 147-175 but X=SO						
182[1]	S	H	4-Cl	H	H	H	3-OBz
183[1]	S	H	4-Cl	H	H	H	3-OCOCH(Me)$_2$
184[1]	S	Ac	H	H	7-F	H	3-OAc
185[1]	S	Me	H	H	7-Me	H	3-OMe
186[1]	S	H	H	H	7-F	H	3-OAc
187[1]	S	Me	H	H	9-Cl	H	3-OMe
188[1]	S	Me	H	H	9-Cl	H	3-OAc
189[1]	S	Me	H	H	7-Me	H	3-OAc

TABLE I (cont'd)

Compound	X	R^1	R^2	R^3	R^4	R^5	T
190[1]	S	H	H	H	9-Cl	H	3-OAc
191[1]	S	H	H	4-CF_3	H	H	3-OAc
192[1]	S	H	H	4-Cl	H	H	3-OTs
193[1]	S	Ac	H	4-Cl	7-F	H	3-OMe
194[1]	S	Ac	H	4-Cl	7-F	H	3-OH
195[1]	S	Me	H	4-Cl	7-F	H	3-OMe
196[1]	SO	H	H	H	H	H	3-OAc
197[1,2]	SO_2	H	H	H	H	H	3-OAc
198[1,2]	SO_2	H	H	H	H	H	3-OH
199[1]	SO_2	H	H	H	7-F	H	3-OAc
200[1]	SO_2	H	H	4-Cl	H	H	3-OTs
201[1]	S	H	1-OMe	2-OMe	4-Me	H	3-OH
202[1]	S	H	1-OMe	2-OMe	4-Me	H	3-OAc
203[1]	SO_2	H	1-OMe	2-OMe	4-Me	H	3-OH
204[1]	SO_2	H	4-OMe	H	H	H	3-OH
205[1]	S	H	2-OMe	3-OH	4-Br	7-OMe	H
206[1]	S	H	2-OMe	3-OAc	4-Br	7-OMe	H
207[1]	S	H	2-OMe	3-OAc	4-Cl	7-OMe	H
208[1]	SO_2	H	2-OMe	3-OH	4-Br	7-OMe	H
209[1]	S	H	2-OMe	3-OAc	7-OMe	4-Br	H
210[1]	S	H	2-OMe	3-OAc	7-OMe	4-Br	H
211[1]	S	H	2-OMe	3-OBz	7-OMe	4-Br	H
212[1]	S	Me	2-OMe	3-OMe	7-OMe	4-Br	H
213[1]	S	H	2-OMe	3-OMe	7-OMe	4-Br	H
214[1,2]	S	Ac	2-OMe	3-OAc	7-OMe	4-Br	H
215[1,2]	S	Ac	2-OMe	3-OH	7-OMe	4-Br	H
216[1]	S	Ac	2-OMe	3-OMe	7-OMe	4-Br	H
217[1]	S	Me	2-OMe	3-OAc	7-OMe	4-Br	H

TABLE I (cont'd)

Compound	X	R^1	R^2	R^3	R^4	R^5	T
218[1]	S	Me	2-OMe	3-OH	7-OMe	4-Br	H
219[1]	SO_2	H	2-OMe	3-OH	7-OMe	4-Br	H
220[1]	SO_2	H	2-OMe	3-OAc	7-OMe	4-Br	H
221[1]	SO_2	H	2-OMe	3-OAc	7-OMe	4-Br	H
222[1]	SO	H	2-OMe	3-OAc	7-OMe	4-Br	H
223[1]	SO	H	2-OMe	3-OAc	7-OMe	4-Br	H
224	S	H	2-OMe	3-OCO_2Me	4-Br	7-OMe	H
225[1]	S	H	2-OMe	3-OCO_2Et	4-Br	7-OMe	H
226[1,2]	S	H	2-OMe	3-OCO_2CH(Me)OAc	4-Br	7-OMe	H
227[1]	S	H	2-OMe	3-OCO_2CH(Me)OAc	4-Cl	7-OMe	H
228[1]	S	CO_2Me	2-OMe	3-OH	4-Br	7-OMe	H
229[1]	S	CO_2Et	2-OMe	3-OH	4-Br	7-OMe	H
230[1,2]	S	CO_2CH(Me)OAc	2-OMe	3-OH	4-Br	7-OMe	H
231[1]	S	CO_2CH(Me)OAc	2-OMe	3-OH	4-Cl	7-OMe	H
232[1]	S	CO_2CH(Me)OAc	2-OMe	3-OH	4-F	7-OMe	H
233[1,2]	S	CO_2CH(Me)OAc	2-OMe	3-OAc	4-Br	7-OMe	H
234[1]	S	CO_2CH(Me)OAc	2-OMe	3-OCO_2CH(Me)OAc	4-Br	7-OMe	H
235[1,2]	O	Ac	2-OMe	3-OH	4-Br	7-OMe	H
236[1,2]	O	Ac	2-OMe	3-OAc	4-Br	7-OMe	H
237[1,2]	O	CO_2CH(Me)OAc	2-OMe	3-OH	4-Br	7-OMe	H
238[1]	O	CO_2CH(Me)OAc	2-OMe	3-OAc	4-Br	7-OMe	H
239[1]	S	H	2-OMe	3-OH	4-Br	7-Me	H
240[1]	S	H	2-OMe	3-OAc	4-Br	7-Me	H
241[1]	S	H	2-OMe	3-OH	4-Br	7-F	H
242[1]	S	H	2-OMe	3-OAc	4-Br	7-F	H

TABLE I (cont'd)

	X	R^1	R^2	R^3	R^4	R^5	I
243	S	H	H	H	H	H	OCOEt
244	S	H	2-Cl	3-Cl	H	H	OCO-n-Pr
245	S	H	H	4-Cl	H	H	OCO-n-Bu
246	S	H	1-Me	H	H	H	H
247	S	H	2-CF_3	H	H	H	H
248	S	H	2-Et	H	H	H	H
249	S	H	H	3-Cl	7-OMe	H	H
250	S	H	H	3-Cl	7-Cl	H	H
251	S	H	H	3-NO_2	H	7-NO_2	H
252	S	H	3-NMe_2	H	H	7-NMe_2	H
253	S	H	1-OH	H	H	H	H
254	S	H	3-OAc	7-F	H	H	H
255	S	H	3-CH_2COMe	4-Cl	H	H	H
256	S	H	3-$OCOCHMe_2$	H	4-Cl	H	H
257	S	Ac	3-OMe	4-Cl	H	H	H
258	O	H	2-CF_3	H	H	H	H
259	S	Me	H	3-OMe	H	4-Cl	H
260[1]	SO_2	H	4-Cl	3-OH	H	H	H
261	S	Me	7-F	4-Cl	3-OMe	H	H
262	S	Me	3-OMe	7-Me	H	H	H
263	S	Ac	4-Cl	H	H	H	H
264	S	Ac	3-OAc	4-Cl	H	H	H
265	SO_2	Ac	4-Cl	H	H	H	3-OH
266	SO_2	Ac	4-Cl	H	H	H	3-OAc
267[1]	SO_2	Ac	4-Br	H	H	H	3-OAc

TABLE I (cont'd)

	X	R^1	R^2	R^3	R^4	R^5	I
268[1]	SO_2	$CO_2CH(Me)OAc$	4-Cl	H	H	H	3-OH
269[1]	SO_2	H	4-Cl	H	H	3-$OCO_2CH(Me)OAc$	H
270[1]	O	Ac	4-Cl	H	H	H	3-OAc
271[1]	O	$CO_2CH(Me)OAc$	4-Cl	H	H	H	3-OH
272[1]	O	$CO_2CH(Me)OAc$	4-Cl	H	H	H	3-OAc
273[1]	O	H	4-Cl	H	H	3-$OCO_2CH(Me)OAc$	H
274[1]	S	CH_2OAc	4-Cl	H	H	H	3-OAc
275[1,2]	S	CH(Me)OAc	4-Cl	H	H	H	3-OAc
276[1]	S	H	2-OMe	3-OH	7-OH	H	H
277[1]	S	H	2-OMe	3-OH	7-OH	4-Br	H
278[1]	S	H	2-OMe	3-OAc	7-OH	4-Br	H
279[1]	S	H	2-OMe	3-OAc	7-OAc	4-Br	H

TABLE I (cont'd)

Compound	X	R^1	R^2	R^3	R^4	R^5	I
280[1,2]	S	Ac	2-OMe	3-OH	7-OH	4-Br	H
281[1]	S	Ac	2-OMe	3-OAc	7-OH	4-Br	H
282[1]	S	Ac	2-OMe	3-OAc	7-OAc	4-Br	H
283[1,2]	S	Ac	2-OMe	3-OH	7-OAc	4-Br	H
284[1,2]	SO_2	Ac	2-OMe	3-OH	4-Br	7-OMe	H
285[1]	SO_2	$CO_2CH(Me)OAc$	2-OMe	3-OAc	4-Br	7-OMe	H
286[1]	SO_2	Ac	2-OMe	3-OCO$_2$CH(Me)OAc	4-Br	7-OMe	H
287[1,2]	SO_2	Ac	2-OMe	3-OAc	4-Br	7-OMe	H
288[1,2]	SO_2	$CO_2CH(Me)OAc$	2-OMe	3-OH	4-Br	7-OMe	H
289[1,2]	S	Ac	2-OEt	3-OAc	4-Cl	H	H
290[1,2]	S	Ac	2-OEt	3-OH	4-Cl	H	H
291[1]	S	Me	H	7-AC	H	H	3-OMe
292[1]	S	Me	H	H	7-F	H	3-OMe
293[1]	S	Ac	H	H	7-F	H	3-OMe
294[1]	S	Ac	H	H	7-F	H	3-OH

Compound	X	R^1	R^2	R^3	R^4	R^5	I
295	S	H	2-OMe	4-I	7-OMe	H	3-OH
296	S	H	2-OMe	4-CN	7-OMe	H	3-OH
297	S	H	2-OEt	4-Br	7-OEt	H	3-OH
298	S	H	2-OEt	4-Cl	7-OEt	H	3-OH
299	S	H	2-OMe	4-Br	7-OEt	H	3-OH
300	S	H	2-OMe	4-Cl	7-OEt	H	3-OH
301	S	H	2-OMe	4-F	7-OEt	H	3-OH
302	S	H	2-OEt	4-Br	7-OMe	H	3-OH
303	S	H	2-OEt	4-Cl	7-OMe	H	3-OH
304	S	H	2-OEt	4-F	7-OMe	H	3-OH
305	S	H	2-OEt	4-CF_3	7-OMe	H	3-OH

The compounds of the Formula I have unexpected activity as inhibitors of the mammalian biosynthesis of both leukotriene B_4, as well as leukotrienes C_4, D_4, E_4 and F_4, the active elements of slow reacting substance of anaphylaxis (SRS-A). This inhibition of the biosynthesis of leukotrienes indicates that the compositions would be useful to treat. prevent or ameliorate, in mammals and especially in humans 1) pulmonary conditions including diseases such as asthma, 2) allergies and allergic reactions such as allergic rhinitis, contact dermatitis. allergic conjunctivitis and the like, 3) inflammation such as arthritis, 4) pain, 5) skin conditions such as psoriasis and the like and 5) cardiovascular conditions such as angina and the like.

Representative compounds of Formula I have been tested using one or more of the following assays to determine their mammalian leukotriene biosynthesis inhibiting activity and other relevant activities.

Mouse Macrophage Assay

Mouse peritoneal macrophages were treated sequentially with arachidonic acid (labelled with tritium): the compound being evaluated as an inhibitor, and a stimulator (zymosan). Metabolites derived from arachidonic acid (PGE_2, 6-Keto $PG\text{-}F_{1\alpha}$ and Leukotriene C_4) were separated from the incubation medium by extraction and chromatography, and then quantitated by determining the amount of radioactivity (cpm) associated with each of them. Inhibitors caused a reduction in the amount of radioactivity (cpm) associated with a given metabolite. (This protocol is identical to that described in the reference except that the radioactivity herein associated with the LTC_4 was determined by counting an aliquot of the final aqueous solution directly rather than chromatographing it first).

Reference: Humes. J.L. et al., J. Biol. Chem. 257, 1591-4 (1982).

Antigen Challenge 'in vitro' Assay

Male guinea pigs weighing 300-350 g were sensitized by injecting (i.p.) 0.5 ml of a suspension containing 0.4 mg of egg albumin (Ovalbumin, Grade V, Sigma Chemical Co.) and 4.0 g aluminum hydroxide in 19.6 ml of saline. Two weeks were permitted for sensitization to occur.

Three sensitized guinea pigs were stunned and exsanguinated. The tracheas were removed, freed of adhering tissue and divided longitudinally by cutting through the cartilaginous tissue directly opposite the muscle insertion. Each opened trachea was then transected between every second cartilage. Four of the cut sections were tied together. end to end in a series with No. 0.7 silk thread ensuring that the tracheal muscles were all in the same vertical plane. Thus, each chain consisted of tissue from three different animals.

The chain so formed was then suspended under 1 g of tension (by silk ties at each end) in a 20 ml

organ bath containing 10 ml of modified [1] Krebs-Henseleit buffer solution gassed with 95% O_2 and 5% CO_2 at 37° C. Mepyramine (0.55 μg/ml) and indomethacin (2.67 μg/ml were added to the buffer to avoid the contribution of histamine receptors and cyclooxygenase products to the contraction. To record responses one end of the tracheal chain was attached to a Gould Statham UC-2 force displacement transducer which was connected to a Beckman Type R-dynograph. The preparations were allowed to equilibrate for one hour during which time the tissues were automatically washed (10 ml volume displacement) every 6 minutes.

After the equilibration period the tissues were primed with methacholine (3 μg/1ml; 1.5 x 10^{-5}M), washed and allowed to recover to baseline. The tissues were treated again with a second dose of methacholine, washed, allowed to return to baseline and washed for an additional hour.

Two chains were used as a control. These were incubated in a concentration of egg albumin sufficient to induce an average contraction of 50-80% of the methacholine response.

Each compound to be tested was added to two other baths (at a final concentration in each bath of 10 μg/ml or lower) 15 minutes prior to challenging the fresh chains with egg albumin.

The response of the challenged tissue was expressed as a percentage of the methacholine maximum. The % inhibition for each compound was then calculated. Compounds which at 10 μg/ml (final concentration) inhibited the egg albumin response by 50% or more were retested at a lower concentration.

RAT POLYMORPHONUCLEAR LEUKOCYTE (P.M.N.) Assay

Rats under ether anesthesia are injected (i.p.) with 8 ml of a suspension of sodium caseinate (6 grams in ca. 50 ml water). After 15-24 hours the rats are sacrificed (CO_2) and the cells from the peritoneal cavity are recovered by lavage with 20 ml of buffer (Eagles MEM containing 30 mM HEPES adjusted to pH 7.4 with NaOH). The cells are pelleted (350 x g, 5 min.), resuspended in buffer with vigorous shaking, filtered through lens paper, recentrifuged and finally suspended in buffer at a concentration of 10 cells/ml. A 500 μl aliquot of PMN suspension and test compound are preincubated for 2 minutes at 37° C, followed by the addition of 10 μM A-23187. The suspension is stirred for an additional 4 minutes then bioassayed for LTB_4 content by adding an aliquot to a second 500 μl portion of the PMN at 37° C. The LTB_4 produced in the first incubation causes aggregation of the second PMN, which is measured as a change in light transmission. The size of the assay aliquot is chosen to give a submaximal transmission change (usually ~70%) for the untreated control. The percentage inhibition of LTB_4 formation is calculated from the ratio of transmission

change in the sample to the transmission change in the compound-free control.

Results from the assays described above for several compounds of Formula I are shown in Table II.

1 modified Krebs solution in grams/liter and (mM): NaCl-6.87 (120); glucose-2.1 (11); $NaHCO_3$-2.1 (25); KCl-0.32 (4.72); $CaCl_2$-0.28 (2.5); $MgSO_4.7H_2O$-0.11 (0.5); KH_2PO_4-0.16 (1.2); pH of bathing solution- 7.35 ± 0.05

TABLE II

ASSAY RESULTS

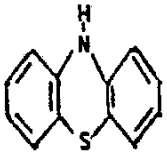
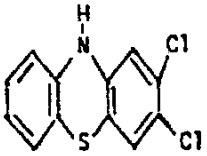
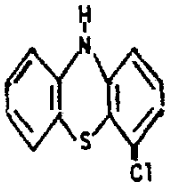
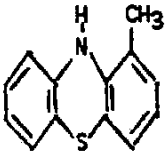
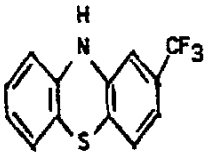
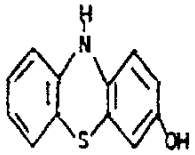
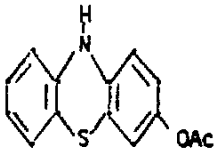
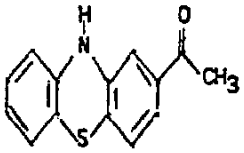
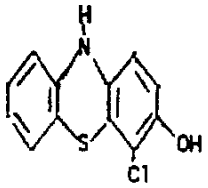
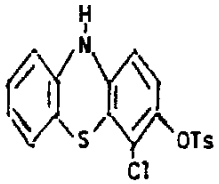
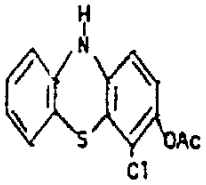
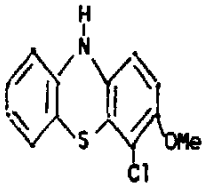
Compound		Macrophage IC_{50} (µg/ml)	P.M.N. IC_{50} (µg/ml)	In Vitro Antigen Challenge % Inhibition at concentration in parenthesis (µg/ml)
1		0.06	0.4	100% (10)
2		0.04	-	-
3		0.01-0.1	0.05-0.5	37% (10)
4		5	-	76% (10)
5		0.1	-	7% (10)

TABLE II (cont'd)

6		0.1–1	0.016	100 (10) 47 (1)
7		0.01–0.1	0.005	60 (10)
8		0.2	-	60 (10)
9		-	0.005	97 (3)
10		-	0.1–1	14 (3)
11		0.1	92%[1]	100 (10) 62 (1)
12		-	0.01–0.1	60 (1)

[1] Percentage inhibition at 5 µg/ml.

TABLE II (cont'd)

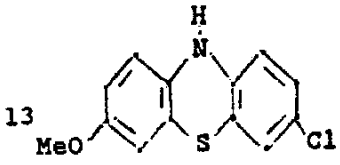
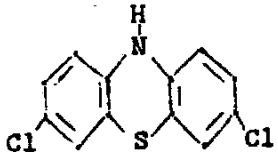
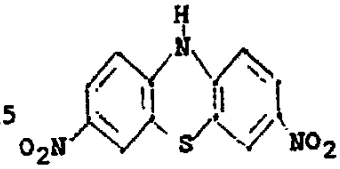
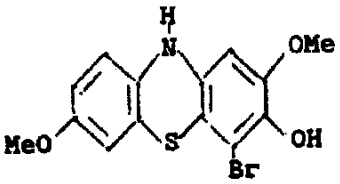
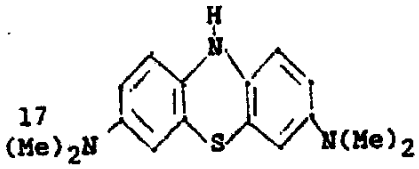
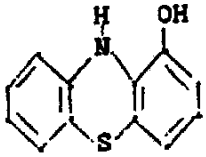
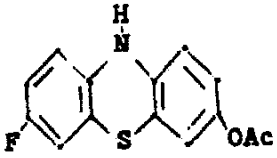
13		0.12	-	22 (10)
14		0.01-0.1	0.005-0.05	1 (10)
15		0.0016-0.008	-	21 (10)
16		-	0.01	-
17		5	-	-
18		-	0.05-0.5	3 (10)
19		-	0.005	-

TABLE II (cont'd)

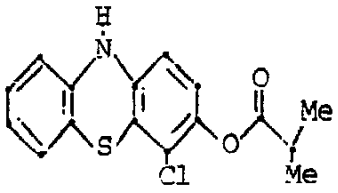
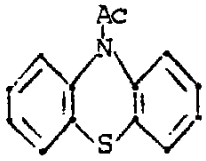
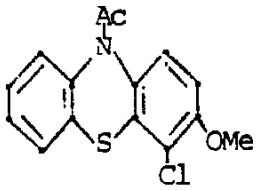
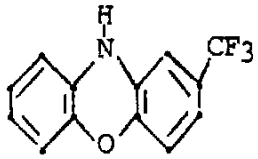
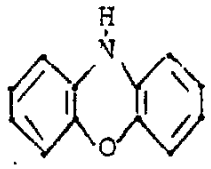
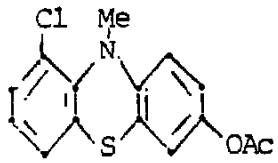
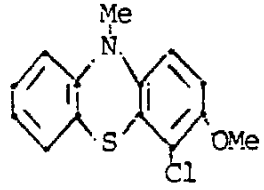
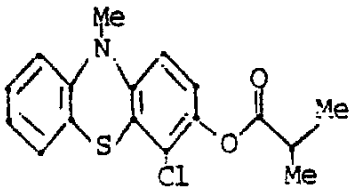
20		-	0.005-0.05	65 (10)
21		5	-	-
22		1.0	1.0	91 (10)
23		-	0.05-0.5	40 (3)
24		0.1	5	88% (1)
25		-	0.5	1-9% (3)
26		1	5	3% (10)

TABLE II (cont'd)

27		-	0.005-0.05	6% (3)

In addition to the assay results described in Table II, the following assays were employed to determine the effectiveness of selected compounds of Formula I as antiasthma and analgesia agents.

Asthmatic Rat Assay

Rats were obtained from an inbred line of asthmatic rats. Both female and male rats from 200 to 300 g were used.

Egg albumin (EA), grade V, crystallized and lyophilized, was obtained from Sigma Chemical Co., St. Louis. Bordetella pertussis vaccine, containing 30 x 10^9 killed bacteria per ml was obtained from the Institut Armand-Frappier, Laval des Rapides, Quebec. Aluminum hydroxide was obtained from the Regeis Chemical Company, Chicago.

The challenge and subsequent respiratory recordings were carried out in a clear plastic box with internal dimensions 10 x 6 x 4 inches. The top of the box was removable; in use, it was held firmly in place by four clamps and an airtight seal was maintained by a soft rubber gasket. Through the center of each end of the chamber a Devilbiss nebulizer (No. 40) was inserted via an airtight seal and each end of the box also had an outlet. A Fleisch No. 0000 pneumotachograph was inserted into one end of the box and coupled to a Grass volumetric pressure transducer (PT5-A) which was then connected to a Beckman Type R Dynograph through appropriate couplers. While aerosolizing the antigen, the outlets were open and the pneumotachograph was isolated from the chamber. The outlets were closed and the pneumotachograph and the chamber were connected during the recording or the respiratory patterns. For challenge, 2 ml of a 3% solution of antigen in saline was placed into each nebulizer and the aerosol was generated with air from a small Potter diaphragm pump operating at 10 psi and a flow of 8 liters/minutes.

Rats were sensitized by injecting (s.c.) 1 ml of a suspension containing 1 mg EA and 200 mg aluminum hydroxide in saline. Simultaneously, they received an injection (i.p.) of 0.5 ml of B. pertussis vaccine. They were used between days 14 and 18 postsensitization. In order to eliminate the serotonin component of the response, rats were pretreated intravenously 5 minutes prior to aerosol challenge with 30 gm kg^{-1} methylserzide. Rats were then exposed to an aerosol of 3% EA in saline for exactly 1 minute, then their respiratory profiles were recorded for a further 25-30 minutes. The duration of continuous dyspnoea was measured from the respiratory recordings.

Compounds were generally administered either intraperitoneally 1 hour prior to challenge or orally 1-1/2 hours prior to challenge. They were either dissolved in dimethylsulfoxide or suspended in 0.1% methocel and 0.5% Tween 80. The volume injected has 2 ml kg^{-1} (intraperitoneally) or 10 ml kg^{-1} (orally). Prior to oral treatment rats were starved overnight. Their activity was determined in terms of their ability to decrease the duration of symptoms of dyspnoea in comparison with a group of vehicle-treated controls. Usually, a compound was evaluated at a series of doses and an ED_{50} was determined. This was defined as the dose (mg/kg) which would inhibit the duration of symptoms by 50%.

PAF-Induced Hyperalgesia Assay

Female Sprague-Dawley rats, 35-40 g were fasted overnight. Platelet activating factor, PAF, (L-lecithin B-acetyl O-alkyl) 1 µg/0.1 ml was given by subplantar injection in the rat paw. The compounds to be evaluated were homogenized in aqueous Vehicle (0.9% benzyl alcohol, 0.5% Tween 80 and 0.4% methylcellulose) and administered orally in a volume of 0.1 ml, 30 minutes prior to PAF.

Animals were tested 1, 2, 3 and 4 hours after PAF administration. The vocalization threshold, defined as the pressure (mm Hg) needed to evoke a squeak response, was recorded for both the injected and contralateral paw. No animal was subjected to pressure greater than 60 mm Hg. Hyperalgesia is defined as

a decrease in vocalization threshold as compared to a normal paw. Percent inhibition of hyperalgesia was calculated as the proportion of animals with vocalization thresholds greater than 200% of controls.

Results for the assays described above for several compounds of Formula I are shown in Table III.

TABLE III

ASSAY RESULTS

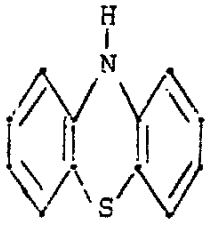
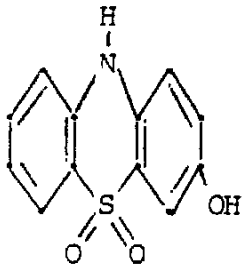
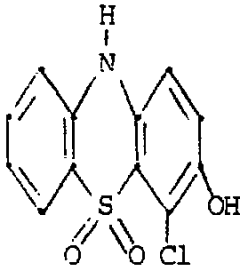
Compound	Asthmatic Rat Assay % inhibition and dose	PAF Induced Hyperalgesia Assay % inhibition and dose
	53% (0.5 mg kg^{-1} p.o.)	50% (3 mg kg^{-1} p.o.)
	70% (3 mg kg^{-1} p.o.)	60% (3 mg kg^{-1} p.o.)
	59% (1.5 mg kg^{-1} p.o.)	50% (1.2 mg kg^{-1} p.o.)

TABLE III (cont'd)

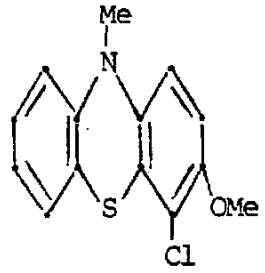
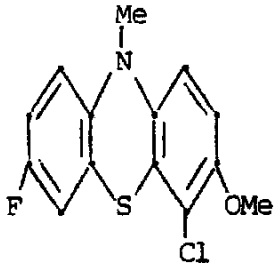
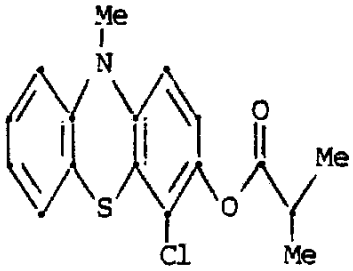
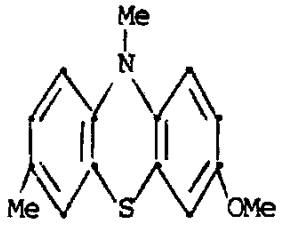
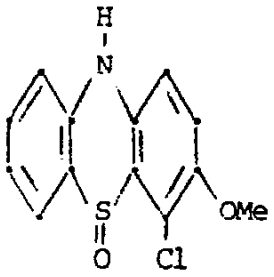
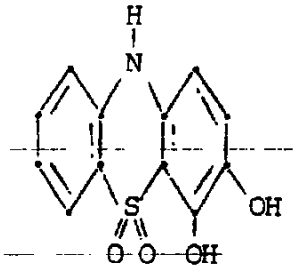
	50% (0.2 mg kg^{-1} p.o.)	50% (0.016 mg kg^{-1} p.o.)
	42% (3 mg kg^{-1} p.o.)	-
	35% (3 mg kg^{-1} p.o.)	70% (1 mg kg^{-1} p.o.)
	58% (3 mg kg^{-1} p.o.)	30% (1 mg kg^{-1} p.o.)

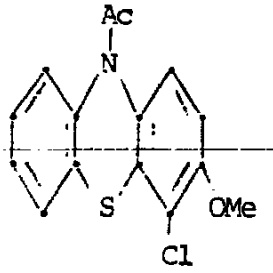
TABLE III (cont'd)



56%
(3 mg kg^{-1} p.o.)

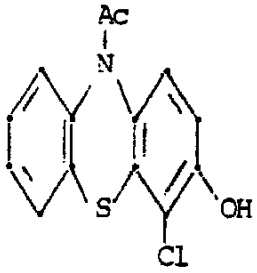


65%
(1.5 mg kg^{-1} p.o.)



59%
(1.5 mg kg^{-1} p.o.)

50%
(0.01 mg kg^{-1} p.o.)



61%
(3 mg kg^{-1} p.o.)

TABLE III (cont'd)

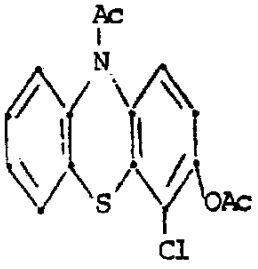
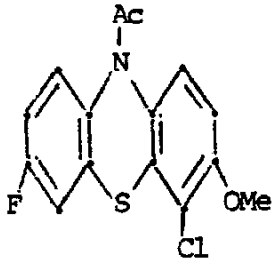
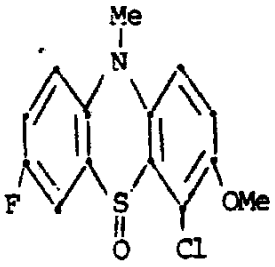
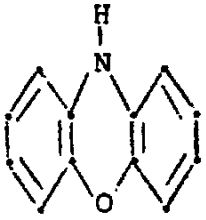
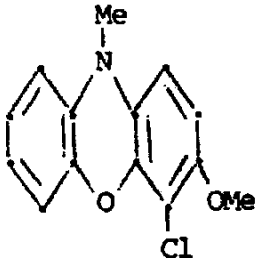
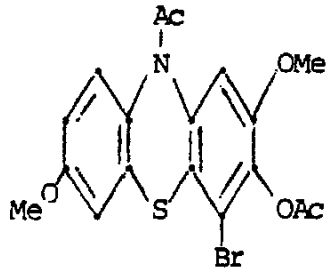
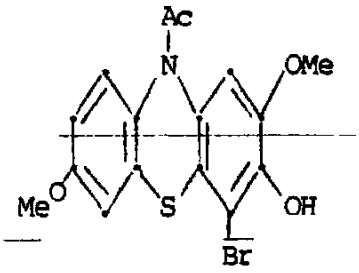
	58% (3 mg kg^{-1} p.o.)	-
	36% (3 mg kg^{-1} p.o.)	-
	52% (3 mg kg^{-1} p.o.)	-
	51% (1.5 mg kg^{-1} p.o.)	-
	49% (0.3 mg kg^{-1} p.o.)	-

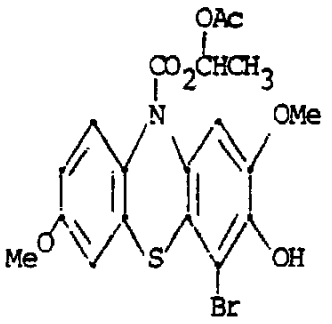
TABLE III (cont'd)



58% (0.5 mg Kg^{-1} p.o.) 60% (0.03 mg Kg^{-1} p.o.)



78% (1.5 mg Kg^{-1} p.o.) 60% (0.1 mg Kg^{-1} p.o.)



42% (5.0 mg Kg^{-1} p.o.) 60% (3.0 mg Kg^{-1} p.o.)

The cytoprotective activity of a compound may be observed in both animals and man by noting the increased resistance of the gastrointestinal mucosa to the noxious effects of strong irritants, for example, the ulcerogenic effects of aspirin or indomethacin. In addition to lessening the effect of non-steroidal anti-inflammatory drugs on the gastrointestinal tract, animal studies show that cytoprotective compounds will prevent gastric lesions induced by oral administration of strong acids, strong bases, ethanol, hypertonic saline solutions and the like.

Two assays can be used to measure cytoprotective ability. These assays are; (A) an ethanol-induced gastric ulcer assay and (B) an indomethacin-induced ulcer assay.

A. Ethanol-Induced Gastric Ulcer

Twenty-four hour fasted Sprague-Dawley (S.D.) rats are perorally (p.o.) dosed with 1.0 ml absolute ethanol. Fifteen to thirty minutes prior to ethanol administration, groups of rats each receive either an aqueous vehicle (aqueous methylcellulose 5% wt.) or the test compound at various doses perorally. One hour later, the animals are sacrificed and stomach mucosae are examined for resulting lesions.

B. Indomethacin-Induced Ulcer Assay

Indomethacin, 10 mg/kg p.o., is used to induce ulcers in 24 hour fasted S.D. rats. Fifteen minutes prior to indomethacin administration, groups of rats each receive either an aqueous vehicle (5% by weight methylcellulose) or the test compound at various doses perorally. Four hours later the animals are sacrificed and stomach mucosae are examined for resulting ulcers.

The pharmaceutical compositions will contain a sufficient amount of a compound of Formula I in a dosage form suitable for inhibiting the mammalian biosynthesis of leukotrienes or, for the treatment desired. The effective concentration of a Formula I compound in the composition will vary as required by the nature and the severity of the condition to be treated, the particular compound selected, the mode of administration, the dosage form and the pharmacological effect and level desired.

Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a leukotriene antagonist. For example, oral, rectal, transdermal, parenteral, intramuscular, intravenous and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules and the like.

A general daily dosage of a Formula I compound for anti-asthmatic, anti-allergic, anti-inflammatory and, generally, uses other than cytoprotection will range from about 10 μg/kg to 20 mg/kg of body weight. A preferred daily dosage range is from 50 μg/kg to 20 mg/kg and a most preferred dosage range is from 100 μg/kg to 10 mg/kg.

The exact amount of a compound of the Formula I to be used as a cytoprotective agent will depend on, inter alia, whether it is being administered to heal damaged cells or to avoid future damage, on the nature of the damaged cells (e.g., gastro-intestinal ulcerations vs. nephrotic necrosis), and on the nature of the causative agent. An example of the use of a compound of the Formula I in avoiding future damage would be co-administration of a compound of the Formula I with a non-steroidal anti-inflammatory drug (for example, indomethacin) that might otherwise cause such damage. For such use, the compound of Formula I is administered from 30 minutes prior up to 30 minutes after administration of the NSAID. Preferably, it is administered prior to or simultaneously with the NSAID.

The effective daily dosage level for compounds of Formula I inducing cytoprotection in mammals, especially humans, will generally range from 0.002 mg/kg to 100 mg/kg, preferably from 0.02 mg/kg to 30 mg/kg. The dosage may be administered in single or divided individual doses.

The pharmaceutical compositions of the present invention comprise a compound of formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include sodium, potassium, lithium, ammonium, calcium, magnesium, ferrous, zinc, copper, manganous, aluminum, ferric, manganic salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, N,N¹-dibenzyl-ethylenediamine, morpholine, N-ethyl morphine, and polyamine resins.

When the compound of Formula I is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include hydrochloric, hydrobromic, sulfuric, nitric, isethionic, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, acetic, benzoic, camphorsulfonic, citric, fumaric, gluconic, glutamic, lactic, malic, maleic, mandelic, mucic, pamoic, pantothenic, phosphoric, succinic and tartaric acids. Particularly preferred are hydrochloric, hydrobromic, citric, maleic, phosphoric, sulfuric and tartaric acids. For a helpful discussion of pharamceutical salts see S.M. Berge et al., Journal of Pharmaceutical Sciences, 66, 1-19(1977).

The compositions include compositions suitable for oral, rectal, ophthalmic, pulmonary, nasal, dermal, topical or parenteral (including subcutaneous, intramuscular and intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

For treating pulmonary conditions such as asthma, the mode of administration may be, for example, oral, parenteral, by inhalation or by suppository. Suitable oral dosage forms are tablets, elixirs, emulsions, solutions, and capsules, including delayed or sustained-release capsules. Parenteral dosage forms include solutions and emulsions. Dosage forms for administration by inhalation include sprays and aerosols. These inhalation fomulations may be administered in metered dosages ranging from 0.1 μ to 200 μg, administered as needed.

For treating allergies or allergic reactions, such as allergic conjunctivitis and allergic rhinitis, the Formula I compound may be administered by any conventional mode, e.g. orally, parenterally, topically, sub-

cutaneously or by inhalation.

The oral and parenteral dosage forms are the same type as for the pulmonary treatment. The topical application dosage forms include ointments, salves, controlled-release patches, emulsions, solutions, thixotropic formulations, powders and sprays. For topical application, the percent by weight of the active ingredient (Formula I compound) may vary from about 0.001 to about 10%.

For treating inflammation the mode of administration may be oral, parenteral or by suppository. The various dosage forms are the same as those described above.

For treating skin diseases such as psoriasis, atopic dermatitis and the like, oral, topical or parenteral administration is useful. For topical application to the diseased area, salves, patches, controlled-release patches and emulsions are convenient dosage forms.

For use as an analgesic, i.e. for treating pain, any suitable mode of administration may be used, e.g., oral, parenteral, by insufflation, or by suppository.

For treating cardiovascular conditions such as angina pectoris, any suitable mode of administration, e.g. oral, parenteral, topical, or by insufflation, and dosage form e.g. pills, liquid formulations, controlled-release capsules, and controlled-release skin patches may be used.

In addition to the common dosage forms set out above, the compound of Formula I may also be administered for the various utilities and indications or for inhibiting leukotriene synthesis by controlled-release means and/or delivery devices such as those described in US Patent Specifications US-A-3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719. Dosage forms for application to treat the eye are also disclosed in US-A-4,348,398.

For intravenous administration, a suitable dosage range for anti-asthmatic, anti-inflammatory or anti-allergic use is from 0.01 mg to 20 mg (preferably from 0.1 mg to 10 mg) of a compound of Formula I per kg of body weight per day and for cytoprotective use from 0.002 mg to 100 mg (preferably from 0.02 mg to 30 mg and especially from 0.1 mg to 10 mg) of a compound of Formula I per kg of body weight per day. In the case of an oral composition, a suitable dosage range for anti-asthmatic, anti-inflammatory or anti-allergic use is, e.g. from 1 to 100 mg of a compounds of Formula I per kg of body weight per day, preferably from 5 mg to 40 mg per kg and for cytoprotective use from 0.01 mg to 100 mg (preferably from 0.1 mg to 30 mg and especially from 0.1 mg to 10 mg) of a compound of Formula I per kg of body weight per day.

For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer. The preferred composition for inhalation is a powder which may be formulated as a cartridge from which the powder composition may be inhaled with the aid of a suitable device. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount.

In practical use, leukotriene inhibitors of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or intravenous. In preparing the compositions for oral dosage form, any of the usual pharmaceutical media are suitable, for example, water, glycols, oils, alcohols, flavouring agents, preservatives, and colouring agents in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, diluents, granulating agents, lubricants, binders and disintegrating agents in the case of oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which the pharmaceutical carriers are obviously solid. If desired, tablets may be sugar-coated or enteric-coated by standard techniques.

Pharmaceutical compositions of the present invention suitable for oral administration and by inhalation in the case of asthma therapy may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from 25 mg to 500 mg of the active ingredient

and each cachet or capsule contains from 25 to 500 mg of the active ingredient.

The following are examples of representative pharmaceutical dosage forms for the leukotriene inhibitors of Formula I:

Injectable Suspension	mg/ml
Compound of Formula I	2
Methylcellulose	5.0
Tween 80	0.5
Benzyl alcohol	9.0
Methyl paraben	1.8
Propyl paraben	0.2
Water for injection to a total volume of 1 ml	

Tablet	mg/tablet
Compound of Formula I	25.0
Microcrystalline Cellulose	325.0
Providone	14.0
Microcrystalline Cellulose	90.0
Pregelatinized Starch	43.5
Magnesium Stearate	2.5
	500

Capsule	mg/capsule
Compound of Formula I	25
Lactose Powder	573.5
Magnesium Stearate	1.5
	600

In addition to the compounds of Formula I, the pharmaceutical compositions of the present invention can also contain other active ingredients, such as cyclooxygenase inhibitors, non-steroidal anti-inflammatory drugs- (NSAIDs), peripheral analgesic agents such as zomepirac diflunisal and the like. The weight ratio of the compound of the Formula I to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the Formula I is combined with an NSAID the weight ratio of the compound of the Formula I to the NSAID will generally range from 1000:1 to 1:1000, preferably 200:1 to 1:200. Combinations of a compound of the Formula I and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

NSAIDs can be characterized into five groups:

(1) the propionic acid derivatives;
(2) the acetic acid derivatives;
(3) the fenamic acid derivatives;
(4) the biphenylcarboxylic acid derivatives; and
(5) the oxicams

or a pharmaceutically acceptable salt thereof.

The propionic acid derivatives which may be used comprise: ibuprofen, ibuprufen aluminum, indoprofen, ketoprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen and bucloxic acid. Structurally related propionic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be included in this group.

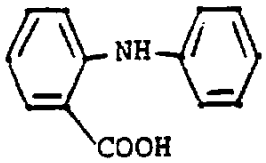
Thus, "propionic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs having a free $-CH(CH_3)COOH$ or $-CH_2CH_2COOH$ group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g., $-CH(CH_3)COO^-Na^+$ or $-CH_2CH_2COO^-Na^+$), typically attached directly or via a carbonyl function to a ring system, preferably to an aromatic ring system.

The acetic acid derivatives which may be used comprise: indomethacin, which is a preferred NSAID, sulindac, tolmetin, zomepirac, diclofenac, fenclofenac, alclofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, and fenclozic acid. Structually related acetic acid derivatives having similar analgesic and anti inflammatory properties are also intended to be encompassed by this group.

Thus, "acetic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs having a free $-CH_2COOH$ group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g. $-CH_2COO^-Na^+$), typically attached directly to a ring system, preferably to an aromatic or heteroaromatic ring system.

The fenamic acid derivatives which may be used comprise: mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid and tolfenamic acid. Structurally related fenamic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

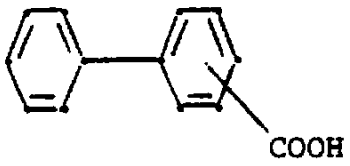
Thus, "fenamic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the basic structure:



which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g., $-COO^-Na^+$.

The biphenylcarboxylic acid derivatives which can be used comprise: diflunisal and flufenisal. Structurally related biphenylcarboxylic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

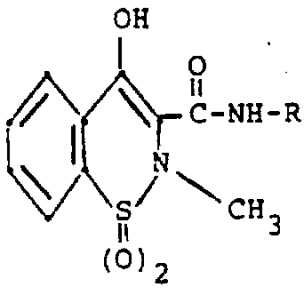
Thus, "biphenylcarboxylic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the basic structure:



which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g., $-COO^-Na^+$.

The oxicams which can be used in the present invention comprise: piroxicam, sudoxicam, isoxicam and 4-hydroxyl-1,2-benzothiazine 1,1-dioxide 4-(N-phenyl)-carboxamide. Structurally related oxicams having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

Thus, "oxicams" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which have the general formula:



wherein R is an aryl or heteroaryl ring system.

The following NSAIDs may also be used: acemetacin, alminoprofen, amfenac sodium, aminoprofen, anitrazafen, antrafenine, auranofin, bendazac lysinate, benzydamine, beprozin, broperamole, bufezolac, carprofen, cinmetacin, ciproquazone, clidanac, cloximate, dazidamine, deboxamet, delmetacin, detomidine, dexindoprofen, diacerein, di-fisalamine, difenpyramide, emorfazone, enfenamic acid, enolicam, epirizole, etersalate, etodolac, etofenamate, fanetizole mesylate, fenclofenac, fenclorac, fendosal, fenflumizole, fentiazac, feprazone, floctafenine, flunixin, flunoxaprofen, fluproquazone, fopirtoline, fosfosal, furcloprofen, furofenac, glucametacin, guaimesal, ibuproxam, isofezolac, isonixim, isoprofen, isoxepac, isoxicam, lefetamine HCl, leflunomide, lofemizole, lonazolac calcium, lotifazole, loxoprofen, lysin clonixinate, meclofenamate sodium, meseclazone, miroprofen, nabumetone, nictindole, nimesulide, orpanoxin, oxametacin, oxapadol, oxprozin, perisoxal citrate, pimeprofen, pimetacin, piproxen, pirazolac, pirfenidone, pirprofen, pranoprofen, proglumetacin maleate, proquazone, pyridoxiprofen, sudoxicam, suprofen, talmetacin, talniflumate, tenoxicam, thiazolinobutazone, thielavin B, tiaprofenic acid, tiaramide HCl, tiflamizole, timegadine, tioxaprofen, tolfenamic acid, tolpadol, tryptamid, ufenamate, and zidometacin.

The following NSAIDS, designated by company code number, may also be used:
480156S, AA 861, AD1590, AFP802, AFP860, A177B, AP504, AU8001, BPPC, Bu540C, CHINOIN 127, CN100, EB382, EL508, F1044, GV3658, ITF182, KCNTEI6090, LA2851, MR714, MR897, MY309, ONO3144, PR823, PV102, PV108, R830, RS2131, SCR152, SH440, SIR 133, SPAS510, SQ27239, ST281, SY6001, TA60, TVX2706, TVX2706, U60257, and WY41770.

The chemical names of these compounds are, respectively,
2-[4-(2-thiazolyloxy)-phenyl]-propionic acid
2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadiynyl-1,4-benzoquinone)
2-(8-methyl-10,11-dihydro-11-oxodibenz[b,f]oxepin-2-yl)propionic acid
3,4,5-trimethoxybenzoyl-ibuprofen
guaiphenesin ibuprofenate
[6-[[1-(3,4-dihydro-8-hydroxy-1-oxo-1H-2-benzopyran-3-yl)-3-methylbutyl]amino]-5-dihydroxy-6-oxo-3-hexanamido]ammonium chloride chlorhexidine dinaproxenate
4' -acetamidophenyl-2-(5'-p-toluyl-1'-methyl-pyrrole)-acetate
(±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid tromethamine salt
3-methylamino-1-[3-(trifluoromethyl)-phenyl]-2-pyrazoline
Chinoin-127, a rimazolium analogue
2-(p-methylallylaminophenyl)propionic acid
(±)-α-[[(2-hydroxy-1,1-dimethylethyl)amino-]methyl]benzyl alcohol
5-[5-(4-chlorophenyl)-2-furanyl]-dihydro-2(3H)-furanone diflunisal lysine salt
3,5-di-t-butyl-4-hydrobenzylidene-γ-butyrolactone imidazole 2-hydroxybenzoate
methyl 5,6-E-5,6-methanoeicosa-7E,9E,11Z,14E-eicosatetranoate
2,4-diamino-7-methyl-pyrazolo(1,5-α)-1,3,5-triazine
2-(2',4'-difluoro-4-biphenyl)oxypropionic acid
3-methyl-3-(4-acetylaminophenoxy)-2,4-dioxobenzocyclo-1-esanone
4-(p-chlorophenyl)-1-(p-fluorophenyl)pyrazole-3-acetic acid
2-aminomethyl-4-t-butyl-6-propionylphenol hydrochloride glycolic acid {o-(2,6-dichloroanilino)phenyl] acetate ester the 3-hydroxyphthalide ester of (±)-1-(p-cholrobenzoyl)-5-methoxy-2-methylindole-3-acetic acid
the phthalidyl ester of diclofenac
2,6-di-t-butyl-4-(2'-thenoyl)phenol 2-[4-(2-oxocyclohexylidenemethyl)phenyl]propionic acid
2-(4-biphenylyl)-4-hexenoic acid

11β,17,21-trihydroxy-6α-methylpregna-1,4-diene-3,20-dione 21-acetate 17-propionate
4-(2-bromo-4,5-dimethoxyphenyl)-octahydro-2H-quinolizin-2-one
N-(2-pyridyl)-2-methyl-4-cinnamoyloxy-2H-1,2,-benzothiazine-3-carboxamide-1, 1-dioxide
17α-ethylthio-9α-fluoro-11β-hydroxy-17β-methylthio-androsta-1,4-diene-3-one 1,1,3-trimethyl-5-phenylbiuret
1-(4-chlorbenzoyl-5-methoxy-2-methyl-1H-indole-3-acetic acid butanediol ester
2-(4-(3-methyl-2-butenyl)phenyl)propionic acid
3-ethyl-1-(3-nitrophenyl)-2,4-[1H,3H]-quinazolindione
6,9-de-epoxy-6,9-(phenylimino)-delta(6,8)-PGI1
1- benzoyl-5-methoxy-2-methylindole-3-acetic acid
(5H-dibenzo[a,d]cyclohepten-5-ylidene)acetic acid.

Finally, NSAIDs which may also be used include the salicylates, specifically aspirin, and the phenylbutazones, and pharmaceutically acceptable salts thereof.

Pharmaceutical compositions comprising the Formula I compounds may also contain other inhibitors of the biosynthesis of the leukotrienes such as are disclosed in European Patent Specification EP-A-013848l, -0115394, -0136893, -0140709.

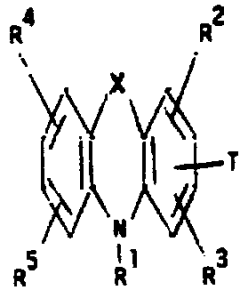
The compounds of the Formula I may also be used in combination with leukotriene antagonists such as those disclosed in EP-A-0106585 and -0104885, and others such as those disclosed in EP-A-0056172 and 0061800; and in United Kingdom Specification GB-A-2,058,785.

Pharmaceutical compositions comprising the Formula I compounds may also contain as the second active ingredient, antihistaminic agents such as benadryl, dramamine, histadyl and phenergan. Alternatively, they may include prostaglandin antagonists such as those disclosed in European Patent Specification EP-A-0011067 or thromboxane antagonists such as those disclosed in US Patent Specification US-A-4,237,160. They may also contain histidine decarboxyase inhibitors such as β -fluoromethylhistidine, described in US-A-4,325,961. The compounds of the Formula I may also be advantageously combined with an H_1 or H_2-receptor antagonist, such as for instance cimetidine, ranitidine, terfenadine, famotidine, and aminothiadiazoles disclosed in EP-A-0040496 and like compounds, such as those disclosed in US Patent Specification US-A-4,283,408; 4,362,736 and 4,394,508. The pharmaceutical compositions may also contain a K^+/H^+ ATPase inhibitor such as omeprazole, disclosed in US Patent Specification US-A-4,255,431.

Another embodiment of the present invention comprises the novel compounds encompassed by Formula I and compounds that are their pharmaceutically acceptable salts. These novel compounds are indicated in Table IV.

TABLE IV

NOVEL COMPOUNDS OF FORMULA I



Compound[a]	X	R^1	R^2	R^3	R^4	R^5	T
1	S	H	4-Cl	H	H	H	3-OH
2	S	H	4-Cl	H	H	H	3-OAc
3[1]	S	Me	4-Cl	H	H	H	3-OMe
4	S	Ac	4-Cl	H	H	H	3-OMe
5	S	H	4-Cl	H	H	H	3-OBz
6	S	H	4-Cl	H	H	H	3-OCOCH(Me)_2
7	S	Me	4-Cl	H	H	H	3-OCOCH(Me)_2
8[1]	S	Ac	4-Cl	H	H	H	3-OAc
9[1]	S	Ac	4-Cl	H	H	H	3-OH
10	SO_2	Me	4-Cl	H	H	H	3-OMe
11	SO	Me	4-Cl	H	H	H	3-OMe
12	S	Me	H	7-Ac	H	H	3-OMe
13	O	Me	4-Cl	H	H	H	3-OAc

[a] The symbol 1 next to the number of a novel compound indicates which compounds are preferred and the symbol 2 next to the number of a novel compound indicates which compounds are also more preferred.

TABLE IV (cont'd)

Compound	X	R^1	R^2	R^3	R^4	R^5	I
14	S	Me	4-Cl	H	H	H	3-OAc
15	S	Me	H	H	7-F	H	3-OMe
16	S	Ac	H	H	7-F	H	3-OMe
17	S	Ac	H	H	7-F	H	3-OH
19	S	Me	H	H	7-Me	H	3-OMe
20	S	H	H	H	7-F	H	3-OAc
21	S	Me	H	H	9-Cl	H	3-OMe
22	S	Me	H	H	9-Cl	H	3-OAc
23	S	Me	H	H	7-Me	H	3-OAc
24	S	H	H	H	9-Cl	H	3-OAc
25	S	H	H	4-CF_3	H	H	3-OAc
26	S	H	H	4-Cl	H	H	3-OTs
27	S	Ac	H	4-Cl	7-F	H	3-OMe
28	S	Ac	H	4-Cl	7-F	H	3-OH
29	S	Me	H	4-Cl	7-F	H	3-OMe
30	S	H	H	2-OEt	4-Cl	H	3-OH
31	SO	H	H	H	H	H	3-OAc
32[1]	SO_2	H	H	H	H	H	3-OAc
33[1]	SO_2	H	H	4-Cl	H	H	3-OAc
34[1]	SO_2	H	H	4-Cl	H	H	3-OH
36	SO_2	H	H	H	7-F	H	3-OAc
37	SO_2	H	H	4-Cl	H	H	3-OTs
38	SO_2	H	H	4-OH	H	H	3-OH
39	S	H	1-OMe	2-OMe	4-Me	H	3-OH
40	S	H	1-OMe	2-OMe	4-Me	H	3-OAc
41[1]	SO_2	H	1-OMe	2-OMe	4-Me	H	3-OH
42	SO_2	H	4-OMe	H	H	H	3-OH

TABLE IV (cont'd)

Compound	X	R^1	R^2	R^3	R^4	R^5	I
43	S	H	1-OH	2-C(Me)$_3$	H	4-C(Me)$_3$	H
44	SO_2	H	1-Cl	H	H	H	3-OH
45	SO_2	Ac	1-Cl	H	H	H	3-OH
46	SO_2	Ac	1-Cl	H	H	H	3-OAc
47	S	Me	1-Cl	H	H	H	3-OAc
48	S	Me	1-Cl	H	H	H	3-OH
49	SO	H	1-OMe	2-OMe	4-Me	H	3-OH
50	SO	H	1-OMe	2-OMe	4-Me	H	3-OAc
51	SO_2	H	1-OMe	2-OMe	4-Me	H	3-OAc
52[1]	S	H	2-OMe	3-OH	4-Br	7-OMe	H
53[1]	S	H	2-OMe	3-OH	4-Cl	7-OMe	H
54[1]	S	H	2-OMe	3-OAc	4-Br	7-OMe	H
55	S	H	2-OMe	3-OAc	4-Cl	7-OMe	H
56	SO_2	H	2-OMe	3-OH	4-Br	7-OMe	H
57	SO_2	H	H	3-OH	H	7-F	H
58	SO_2	H	2-OMe	3-OAc	4-Br	7-OMe	H
59[1]	O	Ac	2-OMe	3-OH	4-Br	7-OMe	H
60[1]	O	Ac	2-OMe	3-OAc	4-Br	7-OMe	H
61[1]	O	$CO_2CH(Me)OAc$	2-OMe	3-OH	4-Br	7-OMe	H
62	O	$CO_2CH(Me)OAc$	2-OMe	3-OAc	4-Br	7-OMe	H
63	S	H	2-OMe	3-OH	4-Br	7-Me	H
64	S	H	2-OMe	3-OAc	4-Br	7-Me	H
65	S	H	2-OMe	3-OH	4-Br	7-F	H
66	S	H	2-OMe	3-OAc	4-Br	7-F	H
67	SO	H	2-OMe	3-OAc	4-Br	7-OMe	H
68	SO_2	H	2-OMe	3-OH	H	7-OMe	H
69	SO_2	H	2-OMe	3-OAc	H	7-OMe	H
70[1,2]	S	Ac	2-OMe	4-Br	7-OMe	H	3-OAc

TABLE IV (cont'd)

Compound	X	R^1	R^2	R^3	R^4	R^5	I
71[1,2]	S	Ac	2-OMe	4-Cl	7-OMe	H	3-OAc
72	S	Ac	2-OMe	4-F	7-OMe	H	3-OAc
73	S	Ac	2-OMe	4-I	7-OMe	H	3-OAc
74	S	Ac	2-OMe	4-CF_3	7-OMe	H	3-OAc
75	S	Ac	2-OMe	4-CN	7-OMe	H	3-OAc
76	S	Ac	2-OEt	4-Br	7-OEt	H	3-OAc
77	S	Ac	2-OEt	4-Cl	7-OEt	H	3-OAc
78	S	Ac	2-OMe	4-Br	7-OEt	H	3-OAc
79	S	Ac	2-OMe	4-Cl	7-OEt	H	3-OAc
80	S	Ac	2-OMe	4-F	7-OEt	H	3-OAc
81	S	Ac	2-OEt	4-Br	7-OMe	H	3-OAc
82	S	Ac	2-OEt	4-Cl	7-OMe	H	3-OAc
83	S	Ac	2-OEt	4-F	7-OMe	H	3-OAc
84	S	Ac	2-OEt	4-CF_3	7-OMe	H	3-OAc
85	S	H	2-OMe	4-Br	7-OMe	H	3-OH
86	S	H	2-OMe	4-Cl	7-OMe	H	3-OH
87[1]	S	H	2-OMe	4-F	7-OMe	H	3-OH
88[1]	S	H	2-OMe	4-CF_3	7-OMe	H	3-OH
89	S	H	2-OMe	4-Br	7-OMe	H	3-OAc
90[1]	S	H	2-OMe	4-Br	7-OMe	H	3-OBz
91[1]	S	H	2-OMe	4-Br	7-OMe	H	3-OCOCHMe$_2$
92[1]	S	H	2-OMe	4-Br	7-OMe	3-OCH_2CO_2H	H
93[1]	S	Ac	2-OMe	4-Br	7-OMe	H	3-OBz
94[1]	S	Ac	2-OMe	4-Br	7-OMe	H	3-OMe
95[1]	S	Ac	2-OMe	4-Br	7-OMe	3-OCH_2CO_2H	H
96[1]	S	Ac	2-OMe	4-Cl	7-OMe	3-OCH_2CO_2H	H
97[1]	S	CH_2OAc	2-OMe	4-Br	7-OMe	H	3-OH
98[1]	S	CH_2OAc	2-OMe	4-Cl	7-OMe	H	3-OH
99[1]	S	CH_2OAc	2-OMe	4-Br	7-OMe	H	3-OAc

TABLE IV (cont'd)

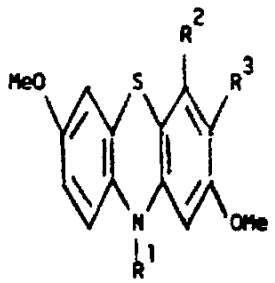
Compound	X	R^1	R^2	R^3	R^4	R^5	I
100[1]	S	CH_2OAc	2-OMe	4-Br	7-OMe	H	3-OBz
101[1]	S	CH_2OAc	2-OMe	4-Br	7-OMe	H	3-OMe
102[1]	S	CH_3	2-OMe	4-Br	7-OMe	H	3-OH
103[1]	S	CH_3	2-OMe	4-Br	7-OMe	H	3-OAc
104[1]	S	CH_3	2-OMe	4-Cl	7-OMe	H	3-OH
105[1]	S	Me	2-OMe	4-F	7-OMe	H	3-OH
106[1]	S	Me	2-OMe	4-CF_3	7-OMe	H	3-OH
107[1]	S	CH(Me)OAc	2-OMe	4-Br	7-OMe	H	3-OH
108[1]	S	CH(Me)OCOC(Me)$_3$	2-OMe	4-Br	7-OMe	H	3-OH
109[1]	S	CH(Me)OAc	2-OMe	4-Cl	7-OMe	H	3-OH
110[1]	S	CH(Me)OAc	2-OMe	4-F	7-OMe	H	3-OH
111[1]	S	CH(Me)OAc	2-OMe	4-CF_3	7-OMe	H	3-OH
112	S	H	2-OMe	4-Br	7-OMe	3-OCO_2Me	H
113	S	H	2-OMe	4-Br	7-OMe	3-OCO_2Et	H
114[1]	S	H	2-OMe	4-Br	7-OMe	3-OCO_2CH(Me)OAc	H
115	S	H	2-OMe	4-Cl	7-OMe	3-OCO_2CH(Me)OAc	H
116	S	CO_2Me	2-OMe	4-Br	7-OMe	H	3-OH
117	S	CO_2Et	2-OMe	4-Br	7-OMe	H	3-OH
118[1,2]	S	CO_2CH(Me)OAc	2-OMe	4-Br	7-OMe	H	3-OH
119[1,2]	S	CO_2CH(Me)OAc	2-OMe	4-Cl	7-OMe	H	3-OH
120	S	CO_2CH(Me)OAc	2-OMe	4-F	7-OMe	H	3-OH
121[1,2]	S	CO_2CH(Me)OAc	2-OMe	4-Br	7-OMe	H	3-OAc
122	S	CO_2CH(Me)OAc	2-OMe	4-Br	7-OMe	3-OCO_2CH(Me)OAc	H
123[1,2]	S	Ac	2-OMe	4-Br	7-OMe	H	3-OH
124	S	Ac	2-OMe	4-Cl	7-OMe	H	3-OH
125	S	Me	2-OMe	4-Br	7-OMe	H	3-OMe
126	S	H	2-OMe	4-Br	7-OMe	H	3-OMe
127[1]	S	CH(Me)OAc	4-Cl	H	H	H	3-OAc
128[1]	SO_2	Ac	4-Cl	H	H	H	3-OH

TABLE IV (cont'd)

Compound	X	R^1	R^2	R^3	R^4	R^5	I
129[1]	SO_2	Ac	4-Cl	H	H	H	3-OAc
130[1]	S	Ac	2-OEt	4-Cl	H	H	3-OH
131[1]	S	Ac	2-OEt	4-Cl	H	H	3-OAc
132[1]	S	Ac	2-OMe	4-Br	7-OH	H	3-OH
133[1]	S	Ac	2-OMe	4-Br	7-OAc	H	3-OH
134[1]	SO_2	Ac	2-OMe	4-Br	7-OMe	H	3-OH
135[1]	SO_2	Ac	2-OMe	4-Br	7-OMe	H	3-OAc
136[1]	SO_2	$CO_2CH(Me)OAc$	2-OMe	4-Br	7-OMe	H	3-OH
137[1,2]	S	CO_2CHOCO (Me; $C(Me)_3$)	H	4-Br	7-OMe	2-OMe	3-OH
138	S	H	2-OMe	4-I	7-OMe	H	3-OH
139	S	H	2-OMe	4-CN	7-OMe	H	3-OH
140	S	H	2-OEt	4-Br	7-OEt	H	3-OH
141	S	H	2-OEt	4-Cl	7-OEt	H	3-OH
142	S	H	2-OMe	4-Br	7-OEt	H	3-OH
143	S	H	2-OMe	4-Cl	7-OEt	H	3-OH
144	S	H	2-OMe	4-F	7-OEt	H	3-OH
145	S	H	2-OEt	4-Br	7-OMe	H	3-OH
146	S	H	2-OEt	4-Cl	7-OMe	H	3-OH
147	S	H	2-OEt	4-F	7-OMe	H	3-OH
148	S	H	2-OEt	4-CF_3	7-OMe	H	3-OH

Some of the compounds described herein contain one or more centers of asymmetry and may thus give rise to diastereoisomers and optical isomers. The present invention includes such possible diastereoisomers as well as their racemic and resolved optically active forms.

Among preferred novel compounds of the present invention are those having the formula:

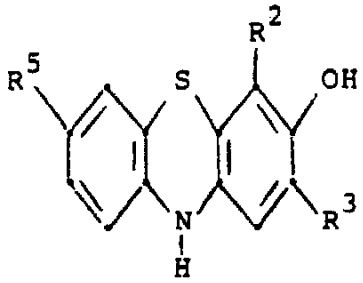


in which the substituents are as set forth in the following table:

R^1	R^2	R^3
H	Br	OH
H	Cl	OH
H	F	OH
H	CF_3	OH
H	Br	OAc
H	Br	OCOPh

R^1	R^2	R^3
H	Br	$OCOCHMe_2$
H	Br	OCH_2CO_2H
Ac	Br	OAc
Ac	Cl	OAc
Ac	Br	OCOPh
Ac	Br	OMe
Ac	Br	OCH_2CO_2H
Ac	Cl	OCH_2CO_2H
CH_2OAc	Br	OH
CH_2OAc	Cl	OH
CH_2OAc	Br	OAc
CH_2OAc	Br	OCOPh
CH_2OAc	Br	OMe
CH_3	Br	OH
CH_3	Br	OAc
CH_3	Cl	OH
CH_3	F	OH
CH_3	CF_3	OH
$CH(CH_3)OAc$	Br	OH
$CH(CH_3)OCOC(CH_3)_3$	Br	OH
$CH(CH_3)OAc$	Cl	OH
$CH(CH_3)OAc$	F	OH
$CH(CH_3)OAc$	CF_3	OH
$CO_2CH(Me)OAc$	Br	OH
$CO_2CH(Me)OAc$	Br	OAc

and those having the formula:

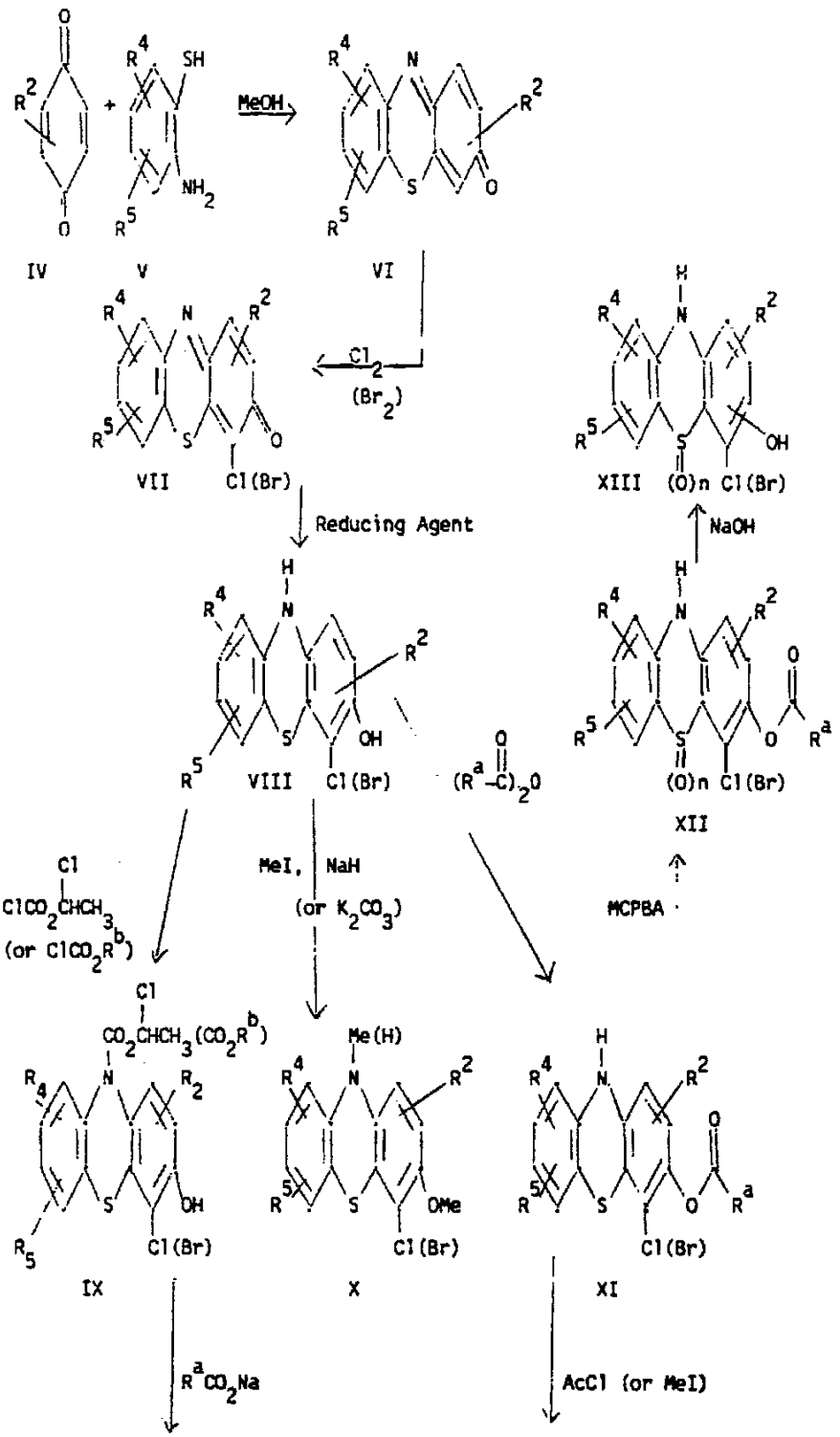


in which the substituents are as set forth in the following table:

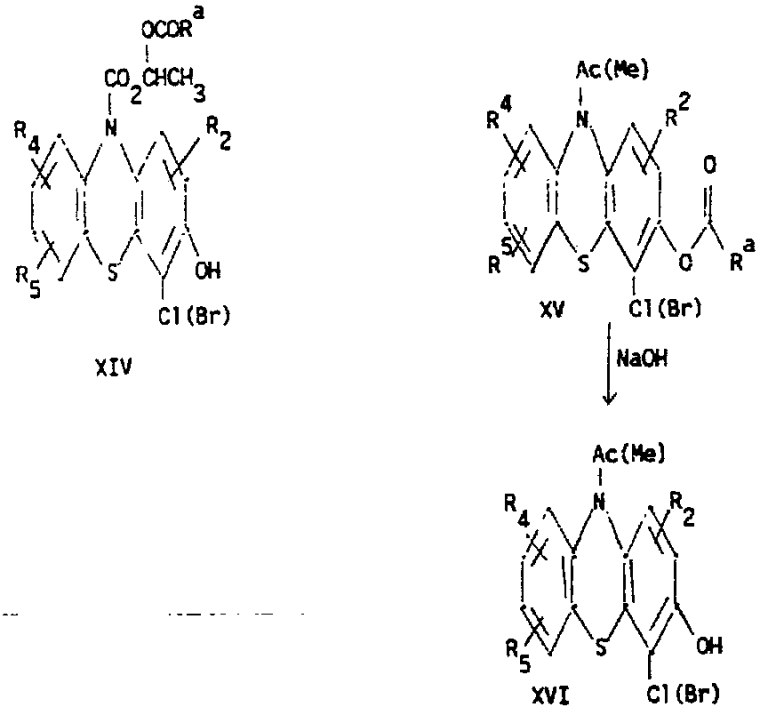
R^2	R^3	R^5
Br	OMe	OMe
Cl	OMe	OMe
F	OMe	OMe
I	OMe	OMe
CF_3	OMe	OMe
CN	OMe	OMe
Br	OEt	OEt
Cl	OEt	OEt
Br	OMe	OEt
Cl	OMe	OEt
F	OMe	OEt
Br	OEt	OMe
Cl	OEt	OMe
F	OEt	OMe
CF_3	OEt	OMe

as well as the compounds 3-acetoxy-10-acetyl-4-chloro-2,7-dimethoxy-10H-phenothiazine and 3-hydroxy-10-(1-acetoxyethoxycarbonyl)-4-chloro-2,7-dimethoxy-10H-phenothiazine.

SCHEME I


MeOH
IV
V
VI
VII
Cl(Br)
Cl2
(Br2)
XIII
(O)n Cl(Br)
NaOH
Reducing Agent
VIII
Cl(Br)
XII
(O)n Cl(Br)
MCPBA
MeI, NaH
(or K2CO3)
ClCO2CHCH3
(or ClCO2Rb)
IX
X
XI
Cl(Br)
Cl(Br)
Cl(Br)
RaCO2Na
AcCl (or MeI)

SCHEME I (cont'd)



where:

R^a is C_1 to C_4 alkyl or phenyl.

R^b is C_1 to C_4 alkyl,

n is 1 or 2.

Reaction of a benzoquinone IV, optimally two equivalents, with 2-aminobenzenethiol V, in a solvent such as acetic acid, acetic acid-water, or a lower alkanol at from -20° to +60° C for 0.25 to 6 hours yields the phenothiazin-3-one VI. Preferably, the solvent is methanol or ethanol, at 0° to 25° C for 0.5 to 2 hours. Halogenation of VI to obtain VII may conveniently be carried out using chlorine or bromine in a lower alkanoic acid such as acetic acid at temperatures of 10° to 50° C. Reduction of VII to VIII is carried out with a reducing agent such as sodium hydrosulfite in a suitable solvent system by stirring at from 10° to 50° C (preferably at room temperature) for 1 to 12 hours (preferably 1 to 4 hours). The solvent system may be a homogeneous one such as dimethylformamide-water or a two-phase system such as ethyl acetate-water or dichloromethane-water.

To prepare a carbamate derivative such as IX, compound VIII is reacted with the appropriate chloroformate reagent in a suitable solvent such as tetrahydrofuran, dioxane or preferably acetonitrile and the mixture heated to reflux for 4 to 24 hours. Reaction of the appropriate chloroalkylcarbamate IX with a metal salt of a carboxylic acid then yields the acyloxyalkoxycarbonyl compound XIV. Preferred salts are those of silver, mercury (II) or sodium, using the corresponding free acid as a solvent, and heating the reaction mixture at 0° to 100° C for from 10 minutes to 2 hours.

To obtain the N,O-dimethylated compounds X, compound VIII is reacted with a methyl halide or a methyl sulfonate (preferably methyl iodide) in the presence of a strong base such as sodium hydride or potassium t-butoxide in a solvent such as tetrahydrofuran or dimethylformamide at 0° to 60° C (preferably room temperature) for from 1 to 24 hours (preferably 1 to 10 hours). The O-methylated compounds X are obtained by substituting a weaker base such as Na_2CO_3 or K_2CO_3 for sodium hydride or potassium t-butoxide, and stirring at room temperature for 0.25 hours to 5 hours.

The O-acyl compounds XI are prepared by reacting compound VIII with the desired acid anhydride in pyridine at a temperature of from -25° to +75° C (preferably 0° to 50° C) for from 1 hour to 24 hours (preferably 4 to 15 hours). Compound XI is transformed into compound XV by reacting it with an acyl halide (bromide or chloride) in a solvent such as dichloromethane, 1,2-dichloroethane or chloroform (preferably dichloromethane) in the presence of 4 Angstrom molecular sieves for a period of 0.5 to 24 hours (preferably

1 to 6 hours) at a temperature of 0° to 60° (preferably room temperature). Hydrolysis of XV to XVI is carried out by reaction with a base such as LiOH, NaOH or KOH, in mixed solvent such as methanol-water or ethanol-water, at from 0° to 60° C (preferably room temperature) for from 5 minutes to 180 minutes (preferably 10 minutes to 90 minutes). Alternatively, the N-acetyl compound XVI can be prepared from VIII by reacting the latter with an acyl halide, such as acetyl chloride, in a solvent such as dimethyl formamide at from 0° to 50° C (preferably room temperature) for from 0.5 to 4 hours depending on the rate of reaction of the particular components.

The N,O-diacyl compound XV can also be prepared directly from VIII by treating a mixture of VIII and the appropriate acyl halide in a solvent such as dimethylformamide at from 50° to 150° C (preferably 75° to 100° C) for from 2 to 24 hours, preferably from 5 hours to 24 hours to ensure completion of the reaction.

The sulfoxide derivatives XII (n = 1) are prepared by treating XI with a peracid such as peracetic acid or meta-chloroperbenzoic acid (MCPBA), in a solvent such as methylene chloride or methylene chloride-methanol for 0.5 to 4 hours at 0° to 30° C. The sulfones XII (n = 2) are obtained by reacting XI with a peracid in methylene chloride-methanol, or preferably, 1,2-dichloroethane-ethanol, at the reflux temperature of the mixture for 12 to 24 hours, depending upon the rate of reaction. Hydrolysis of XII to XIII is carried out in a manner similar to that described for the conversion of XV to XVI.

The following examples are provided to illustrate but not limit the invention. Temperatures are in degrees Celsius.

Some of the 3H-phenothiazin-3-one derivatives used as starting materials are described in our European Patent Application EP-A-0 115 394.

EXAMPLE 1

Synthesis of 3H-phenothiazin-3-one

To a stirring suspension of 1.72 kg (16 mol) of p-benzoquinone in 13 liters MeOH at room temperature was added slowly a solution of 1.0 kg (8 mol) of 2-aminothiophenol in 600 ml MeOH over a period of 1 hour. The resulting red mixture was stirred at room temperature for another 2 hours and then the product 3H-phenothiazin-3-one was filtered off. This 3H-phenothiazin-3-one was washed thoroughly with methanol and dried to give 1.07 kg of 3H-phenothiazin-3-one (61.49% yield) , m.p. 157-159° C.

EXAMPLE 2

Synthesis of 4-chloro-3H-phenothiazin-3-one

To a stirring solution of 500 g (2.34 mol) of 3H-phenothiazin-3-one in 12.5 liters of glacial acetic acid was added 1.25 kg of potassium dichromate. The mixture was stirred at room temperature for 1/2 hour. To this resulting mixture was then added 2.34 mol of a 1M solution of chlorine in glacial acetic acid dropwise over a period of 4 hours. The progress of the reaction was monitored by tlc to ensure no excess chlorine was added. After addition of chlorine was completed the mixture was stirred at room temperature for another 1/2 hour and was then poured into 120 liters of H_2O with vigorous stirring. The 4-chloro-3H-phenothiazin-3-one which precipitated was allowed to settle overnight. The majority of the aqueous solution was siphoned off and discarded and the rest was filtered. The filtered precipitate was washed thoroughly with water and then rinsed with methanol and was allowed to dry to give 504 g crude 4-chloro-3H-phenothiazin-3-one which was recrystallized from toluene. m.p.: 221° C.

EXAMPLE 3

Synthesis of 4-Chloro-3-hydroxy-10H-phenothiazine

A solution of $Na_2S_2O_4$ (70 g) in water (500 ml) was added to a solution of 4-chloro-3H-phenothiazin-3-one (50 g) in DMF (1200 ml). The reaction mixture was stirred at room temperature for 3 hours and then poured in 5 liters of water. The resulting precipitate was then filtered to give the 4-chloro-3-hydroxy-10H-phenothiazine (95 %). m.p.: 110° C.

EXAMPLE 4

Synthesis of 3-acetoxy-4-chloro-10H-phenothiazine

To a solution of 1.8 g of 4-chloro-3-hydroxy-10H-phenothiazine (see Example 3) in 20 ml of acetic anhydride was added 1.2 ml of pyridine. The reaction mixture was then stirred at ambient temperature for 12 hours and then poured in water (75 ml). The resulting precipitate was filtered, washed with water and dried under vacuum to give 1.65 g of 3-acetoxy-4-chloro-10H-phenothiazine (m.p.: 173° C).

EXAMPLE 5

Synthesis of 4-chloro-3-methoxy-10-methyl-10H-phenothiazine

To 25 ml of DMF was added methyl iodide (2.9 ml), 4-chloro-3-hydroxy-10H-phenothiazine (see Example 3) (2.3 g) and sodium hydride (0.672 g). The resulting reaction mixture was stirred at ambient temperature for 12 hours. At 0° C, MeOH was added to destroy the remaining hydride, then H_2O. The resulting solution was extracted with ethyl acetate and the organic phase, dried and evaporated. The resulting residue was then purified by chromatography on silica gel to give 1.5 g of 4-chloro-3-methoxy-10-methyl-10H-phenothiazine (m.p.: 136° C).

EXAMPLE 6

Synthesis 4-chloro-3-methoxy-10-acetyl-10H-phenothiazine

To a solution of 4-chloro-3-acetoxy-10H-phenothiazine (see Example 4) in DMF (10 mls) was added methyl iodide (0.34 ml) and sodium hydride (114 mg). The reaction mixture was stirred at ambient temperature for 12 hours. Methanol and water were then added and the resulting mixture extracted with EtOAc. The organic phases were then collected, dried and evaporated. The resulting residue was purified by chromatography on silica gel (HPLC) to give 0.56 g of 4-chloro-3-methoxy-10-acetyl-10H-phenothiazine (m.p. 136° C).

EXAMPLE 7

Synthesis of 3-benzoyloxy-4-chloro-10H-phenothiazine

To a solution of (0.5 g)4-chloro-3-hydroxy-10H-phenothiazine (see Example 3) in pyridine (4 ml) was added 1.2 g of benzoic anhydride. The reaction mixture was stirred at ambient temperature for 7 hours and then poured in H_2O. The resulting precipitate was then filtered and purified by trituration in $CHCl_3$. The resulting solid material was then filtered and dried under vacuum to give 0.6 g of 3-benzoyloxy-4-chloro-10H-phenothiazine (m.p. 203° C).

EXAMPLE 8

Synthesis of 4-chloro-3-isobutyryloxy-10H-phenothiazine

To a solution of iso-butyric acid (1.6 ml) in THF (10 ml) at 0° C was added Et_3N (2.7 ml) and methylchloroformate (1.5 ml). To this resulting suspension was added slowly at 0° C a solution of 4-chloro-3-hydroxy-10H-phenothiazine in THF (10 ml). The reaction mixture was stirred at 5° C for 12 hours, after which H_2O was added and the resulting aqueous phase extracted with ethyl acetate. The organic layer was then dried and evaporated. The resulting residue was purified by chromatography on silica gel to give 2.25 g of 4-chloro-3-isobutyryloxy-10H-phenothiazine (m.p. 155° C).

EXAMPLE 9

Synthesis of 4-chloro-3-isobutyryloxy-10-methyl-10H-phenothiazine

To a solution of 4-chloro-3-isobutyryloxy--10H-phenothiazine (see Example 8) (202 mg) in DMF (5 ml) was added methyl iodide (0.2 ml) and sodium hydride (18 mg) at 0° C. The reaction mixture was stirred at ambient temperature for 12 hours. To the reaction mixture was added water and the resulting aqueous layer extracted with EtOAc. The organic layers were collected, dried and evaporated to give a residue which was purified by chromatography on silica gel (plates) to give 100 mg of 4-chloro-3-isobutyryloxy-10-methyl-10H-phenothiazine (m.p. 147° C).

EXAMPLE 10

Synthesis of 3-acetoxy-10-acetyl-4-chloro-10H-phenothiazine

To 1.1 g of 3-acetoxy-4-chloro-10H-phenothiazine (see Example 4) was added acetyl chloride (7 ml), DMF (5 ml) and potassium tert-butoxide (0.42 g). The reaction mixture was stirred at ambient temperature for 1 hour and then, poured in water. The resulting precipitate was filtered and purified by chromatography on silica gel to give (1.08 g) 3-acetoxy-10-acetyl-4-chloro-10H-phenothiazine (m.p. 155° C).

EXAMPLE 11

Synthesis of 10-acetyl-4-chloro-3-hydroxy-10H-phenothiazine

To a solution of 4-chloro-3-hydroxyphenothiazine (2.2 g) in DMF (10 ml) was added 10 ml of acetyl chloride. The reaction mixture was stirred at ambient temperature for 1 hour. Ethyl acetate was then added, followed by ice and H_2O. The organic layer was separated, dried and evaporated. The resulting residue was purified by chromatography on silica gel to give 1.4 g of 10-acetyl-4-chloro-3-hydroxy-10H-phenothiazine (m.p. 214° C).

EXAMPLE 12

Synthesis of 4-chloro-5,5-dioxo-3-methoxy-10-methyl-10H-phenothiazine

To 4-chloro-3-methoxy-10-methyl-10H-phenothiazine (see Example 5) (0.33 g) in acetic acid (10 ml) was added hydrogen peroxide (3 ml). The reaction mixture was stirred at 80° C for 2 hours. After cooling to ambient temperature, the resulting precipitate was filtered and washed with acetic acid to give the 4-chloro-5,5-dioxo-3-methoxy-10-methyl-10H-phenothiazine (0.2 g) (m.p. 244° C).

EXAMPLE 13

Synthesis of 4-chloro-3-methoxy-10-methyl-5-oxo-10H-phenothiazine

To 4-chloro-3-methoxy-10methyl-10H-phenothiazine (0.5 g) (see Example 5) was added acetic acid (12 ml) and hydrogen peroxide (2 ml). The reaction mixture was heated at 50° C for 15 minutes and then, evaporated to dryness. The corresponding sulfoxide (0.5 g) (4-chloro-3-methoxy-10-methyl-5-oxo-10H-phenothiazine) was obtained by crystallization (m.p. decomposed at 141° C).

EXAMPLE 14

Synthesis of 2-chloro-3,7-diacetyl-10-methyl-10H-phenothiazine

To 2-chloro-10-methyl-10H-phenothiazine (5 g) in carbon disulfide (100 ml) was added acetyl chloride (2.2 ml) and (portionwise) aluminum chloride (10 g). The reaction mixture was then stirred under reflux for 12 hours. The carbon disulfide was then decanted and the residue treated with ice and concentrated HCl. The resulting precipitate was filtered, washed with water and purified by chromatography on silica gel to yield the title compound, m.p. 185° C.

EXAMPLE 15

Synthesis of 4-chloro-3-methoxy-10-methyl-10H-phenoxazine

This compound was prepared as described in Example 5 following the sequence exemplified in Examples 2 and 3, but starting with 3H-phenoxazine-3-one, instead of 3H-phenothiazine-3-one. The title compound, 4-chloro-3-methoxy-10-methyl-10H-phenoxazine was then obtained (m.p. 107° C).

EXAMPLE 16

Synthesis of 3,4-dihydroxy-10H-phenothiazine-5,5-dioxide

To a suspension of 4-hydroxy-3H-phenothiazine-3-one-5,5-dioxide (0.8 g) in a mixture of water (20 ml) and ethyl acetate (20 ml) there was added sodium dithionite (2 g) and the resulting mixture was stirred at room temperature for 20 minutes. The insoluble solid was then filtered, washed with water and dried to afford the title compound, m.p. (dec.) 261 °C.

Calc'd:	C: 54.74;	H: 3.45;	N: 5.32;	S: 12.18
Found:	C: 54.85;	H: 3.54;	N: 5.26;	S: 12.11

EXAMPLE 17

Synthesis of 2,4-di-t-butyl-1-hydroxy-10H-phenothiazine

To a solution of 3,5-di-t-butyl-1,2-benzoquinone (2.2 a) in methanol (15 ml) cooled in an ice bath was added 2-aminothiophenol (1.38 g) and the mixture was stirred for 2 hours. A solid precipitate was filtered off and crystallized from heptane to yield the title compound m.p. 202-212° (dec.). From the methanol filtrate there was obtained, after chromatography and crystallization, an additional crop of the title compound.

EXAMPLE 18

Synthesis of 4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothiazine

Step 1: Preparation of 2-methoxy-p-benzoquinone

Vanillin (2.432 kg) was added to a solution of sodium hydroxide (640 g) in water (8 1) and cooled to 10 °C with an ice-bath. Then a solution of hydrogen peroxide (30%) (2.4 1) was added at a rate to keep the temperature of the reacting mixture below 30 °C. The addition completed (about 2 hours), the reaction mixture was added over a period of 3 hours to a suspension of sodium periodate (880 g) in water (4 1) and acetic acid (640 ml) cooled with an ice-bath to 10 °C (the temperature of the reacting mixture was kept below 35 °C). The resulting precipitate was filtered, washed with cold water followed by ethanol/hexane (1:1) mixture and air-dried to afford the title compound (1.9 kg), m.p. 144-147 °C.

Step 2: Preparation of 2-amino-5-methoxythiophenol

To a stirred solution of 8N potassium hydroxide (1.3 1) was added 2-amino-6-methoxybenzothiazole (750 g) and the mixture was refluxed overnight. The resulting solution was neutralized by the addition of conc. HCl to pH 8.0, then acetic acid to pH 6.0. The precipitate which formed was filtered and washed with water to afford the title compound which was used immediately in Step 3.

Step 3: Preparation of 2,7-dimethoxy-3H-phenothiazin-3-one

To a suspension of 2-methoxy-p-benzoquinone (1.15 kg) (Step 1) in methanol (8 1) was added portionwise a suspension of 2-amino-5-methoxythiophenol (from Step 2) in methanol (6 1). The reacting mixture was stirred for 15 minutes, filtered and washed with methanol (8 1). The product isolated was swished with DMF (16 1) for 2 hours, filtered and air-dried. The crude material was dissolved in hot DMF (16 1) (130°-140 °C), filtered on Celite and the filtrate cooled to room temperature. The resulting crystals were filtered, washed with methanol (8 1) and air-dried to afford the title compound (70.3 g), m.p. 237-238 °C.

Step 4: Preparation of 4-bromo-2,7-dimethoxy-3H-phenothiazin-3-one

A solution of bromine (280 g) in acetic acid (2.8 1) was added over a period of 30 minutes to a suspension of 2,7-dimethoxy-3H-phenothiazin-3-one (250 g) (Step 3) in acetic acid (7.5 1) and the mixture was stirred for 2 hours. Methanol (12 1) was added over a period of 30 minutes to the reacting mixture and the black suspension was stirred until it became an orange suspension. Then, the precipitate was filtered, washed with methanol and air-dried to afford the desired compound (312 g), m.p. 260-261 °C.

Calc'd: C, 47.74; H, 2.86; N, 3.98; S, 9.10; Br, 22.69.

Observed: C, 47.74; H, 2.81; N, 3.90; S, 9.02; Br, 22.37.

Step 5: Preparation of 4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothiazine

The compound from Step 4 (300 mg) was suspended in ethyl acetate (100 ml) and a solution of $Na_2S_2O_4$ (2 g) in water (40 ml) was then added and the mixture was shaken until the orange-red coloration disappeared. The aqueous layer was decanted, the organic layer was washed with water, dried and evaporated to dryness. The resulting residue was treated with ether and filtered to afford the title compound (240 mg), m.p. 185° C.

Calc'd: C, 47.47; H, 3.42; N, 3.95; S, 9.05; Br, 22.56;

Observed: C, 47.21; H, 3.39; N, 3.74; S, 8.76; Br, 22.44.

EXAMPLE 19

Synthesis of 3-Acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine

Using the procedure of Example 4, but substituting 4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothiazine for 4-chloro-3-hydroxy-10H-phenothiazine, the title compound was obtained. m.p. 201-203° C.

EXAMPLE 20

Synthesis of 3-Acetoxy-2,7-dimethoxy-10H-phenothiazine

Following the procedure of Example 4, but substituting 2,7-dimethoxy-3-hydroxy-10H-phenothiazine for 4-chloro-3-hydroxy-10H-phenothiazine, the title compound was obtained. m.p. 172-174° C.

EXAMPLE 21

Synthesis of 3-Benzoyloxy-4-bromo-2,7-dimethoxy-10H-phenothiazine

Following the procedure described in Example 7, but substituting 4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothiazine for 4-chloro-3-hydroxy-10H-phenothiazine, and heating for 3 hours at 100° C, the title compound was obtained. m.p. 202-203° C.

Calc'd: C, 55.03; H, 3.52; N, 3.05; S, 7.00; Br, 17.44

Found: C, 54.99; H, 3.45; N, 3.06; S, 6.73; Br, 17.57

EXAMPLE 22

Synthesis of 4-Bromo-10-methyl-2,3,7-trimethoxy-10H-phenothiazine

Following the procedure described in Example 5, but substituting 4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothiazine for 4-chloro-3-hydroxy-10H-phenothiazine and potassium t-butoxide for sodium hydride, the title compound was obtained. m.p. 143-145° C.

Calc'd: C, 50.27; H, 4.22; N, 3.66; S, 8.39; Br, 20.91
Found: C, 50.50; H, 4.11; N, 3.67; S, 8.35; Br, 20.83

EXAMPLE 23

Synthesis of 4-Bromo-2,3,7-trimethoxy-10H-phenothiazine

To a solution of 4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothiazine (3.54 g) and methyliodide (2.5 ml) in DMF (20 ml) there was added pulverized potassium carbonate (1.3 g). The reaction mixture was stirred at room temperature. After 15 minutes, another addition of potassium carbonate (1 gram) was made, followed by two other such additions at 15-minute intervals. The final mixture was stirred for a further 15 minutes, then it was diluted with water (100 ml) and ethyl acetate (100 ml). The organic layer was washed twice with water, dried and evaporated down to a solid residue. Crystallization from acetone followed by column chromatography on silica gel eluting with 1:19 ethyl acetate-dichloromethane afforded the pure title compound (1.27 g). m.p. 223-225° C.

Calc'd: C, 48.92; H, 3.83; N, 3.80; S, 8.71; Br, 21.70
Found: C, 48.83; H, 3.76; N, 3.68; S, 8.57; Br, 21.80

EXAMPLE 24

Synthesis of 10-Acetyl-4-Bromo-2,3,7-trimethoxy-10H-phenothiazine

Following the procedure described in Example 6, but substituting 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine for 3-acetoxy-4-chloro-10H-phenothiazine and potassium t-butoxide for sodium hydride, the title compound was obtained. m.p. 147-149° C.

EXAMPLE 25

Synthesis of 3-Acetoxy-4-Bromo-2,7-dimethoxy-10-methyl-10H-phenothiazine and 4-bromo-10-methyl-2,3,7-trimethoxy-10H-phenothiazine

To a solution of 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine (8.0 g) in N,N-dimethylformamide (80 ml) there was added at room temperature methyl iodide (16 ml) and then potassium t-butoxide (3 g). The mixture was stirred at room temperature. Over a period of 24 hours, seven further additions of methyl iodide (10 ml) and potassium t-butoxide (2 g) were made. The final reaction mixture was diluted With ethyl acetate and the solids filtered. The filtrate was washed three times with brine, dried and evaporated. Flash chromatography of the residue on a column of silica gel, eluting with a 1:9 mixture of ethyl acetate and hexane afforded 3-acetoxy-4-bromo-2,7-dimethoxy-10-methyl-10H-phenothiazine (830 mg, m.p. 189-190° C) and 4-bromo-10-methyl-2,3,7-trimethoxy-10H-phenothiazine (2.86 g, m.p. 135-137° C).

EXAMPLE 26

Synthesis of 4-bromo-2,7-dimethoxy-3-hydroxy-10-methyl-10H-phenothiazine

To a suspension of 3-acetoxy-4-bromo-2,7-dimethoxy-10-methyl-10H-phenothiazine (0.5 g) in methanol (300 ml) there was added 2N aqueous sodium hydroxide (300 ml) and the mixture was stirred at room temperature overnight. The heterogenous mixture was then acidified with 1N aqueous HCl solution, and

after stirring for 15 minutes the product filtered. This crude product was purified by flash chromatography on a column of silica gel, eluting with a 1:1 mixture of ethyl acetate and hexane, and the pure title product (211 mg) was obtained. m.p. 154-155° C.

EXAMPLE 27

Synthesis of 3-acetoxy-10-acetyl-4-bromo-2,7-dimethoxy-10H-phenothiazine

Method A: To a solution of 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine (8.0 g) in 1,2-dichloroethane (300 ml) there was added acetyl bromide (1.79 ml) and powdered 4 Angstrom molecular sieves (20 g). The resulting mixture was stirred at room temperature for 2 hours, then filtered. The filtrate was evaporated and the residue co-evaporated with acetone twice. It was then crystallized from dichloromethane-hexane to afford the pure title compound (7.0 g). m.p.: 185-187° C.

Method B: To a solution of 3-hydroxy-4-bromo-2,7-dimethoxy-10H-phenothiazine (180 g) in dimethylformamide (1.2 L) was added acetyl chloride (230 mL) and the resulting solution was heated at 85° C for 18 hours. The excess of acetyl chloride was removed under vacuum and the remaining solution was poured slowly onto an ice-water mixture (1:1) (4L) with good mechanical stirring. The resulting precipitate was filtered, dissolved in dichloromethane, dried over sodium sulfate and concentrated under vacuum. The oily residue was dissolved in ether and left to crystallize overnight. The crystals were filtered to afford the title compound (186 g). A sample (10 g) was recrystallized from ethyl acetate to afford the pure product (7 g).

EXAMPLE 28

Synthesis of 10-acetyl-4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothiazine

A mixture of 10-acetyl-3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine (2.0 g) in methanol (40 ml) and 1N aqueous sodium hydroxide solution (40 ml) was stirred at room temperature for 5 hours. The mixture was then made slightly acidic with 1N aqueous HCl and after 15 minutes the crude product was filtered. Crystallization from ethyl acetate afforded the pure title compound (600 mg), m.p.: dec 235° C.

EXAMPLE 29

Synthesis of 10(1-acetoxyethoxycarbonyl)-4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothiazine

Step 1: Preparation of α-chloroethylchloroformate

To a mixture of ethyl chloroformate (108.5 g) and sulfuryl chloride (138 g), benzoyl peroxide (1 g) was added and the mixture was refluxed for 20 hours. The reaction mixture was distilled and the liquid boiling above 110° was collected. This was then fractionated using a 30 cm column packed with glass helices to give 32 g of pure α-chloroethyl chloroformate (b.p. 118-119°).

Step 2: Preparation of 4-bromo-10-(1-chloroethoxy-carbonyl) -2,7-dimethoxy-3-hydroxy-10H-phenothiazine

A mixture of 4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothiazine (5 g) α-chloroethyl chloroformate (7 g) in THF (50 ml) was refluxed for 18 hours. The mixture was then concentrated to a small volume and flash-chromatographed on a column of silica gel to afford the desired product as a solid which was used directly in the next step.

Step 3: 10(1-acetoxyethoxycarbonyl)-4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothiazine

A mixture of 4-bromo-10-(1-chloroethoxy-carbonyl) -2,7-dimethoxy-3-hydroxy-10H-phenothiazine (1g) and mercuric acetate (1.46g) in glacial acetic acid (30 ml) was stirred and heated at 85° for 10 minutes. After cooling the mixture was diluted with ethyl acetate, washed with water, aqueous $NaHCO_3$ solution, and brine, dried and evaporated. Flash chromatography on a column of silica gel, eluting with a 1:3 mixture of ethyl acetate and hexane, afforded the pure title product (599 mg) m.p.: 162-164° C.

EXAMPLE 30

Synthesis of 3-acetoxy-10-(1-acetoxyethoxycarbonyl)-4-bromo-2,7-dimethoxy-10H-phenothiazine

By following the procedures described in steps 2 and 3 of example 29, substituting 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine for the 3-hydroxy analog, the title compound was obtained. m.p.: 134-135° C.

EXAMPLE 31

Synthesis of 3-acetoxy-4-bromo-2-methoxy-7-methyl-10H-phenothiazine

Following the procedure described in Example 3, but substituting 4-bromo-2-methoxy-7-methyl-3H-phenothiazin-3-one for 4-chloro-3H-phenothiazin-3-one, there was obtained the intermediate 4-bromo-3-hydroxy-2-methoxy-7-methyl-10H-phenothiazine, which when used as starting material in the procedure described in Example 4 afforded the title compound. m.p.: 193-194° C.

EXAMPLE 32

Synthesis of 3-acetoxy-4-bromo-7-fluoro-2-methoxy-10H-phenothiazine

Following the procedure described in example 31, but substituting 4-bromo-7-fluoro-2-methoxy-3H-phenothiazin-3-one for the 7-methyl analog, there was obtained the intermediate 4-bromo-7-fluoro-3-hydroxy-2-methoxy-10H-phenothiazine, which was used as starting material in the procedure described in Example 4 to afford the title compound. m.p.: 224-226° C.

EXAMPLE 33

Synthesis of 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine-5-oxide

To a solution of 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine (10.0 g) in dichloromethane (125 ml) and methanol (125 ml) there was added at room temperature 85% m-chloro peroxybenzoic acid (4.36 g). The mixture was stirred for one hour and the solid was filtered and washed with ether. This crude product was stirred at room temperature in dichloromethane (50 ml) overnight and filtered again to afford pure title product (7.7g). m.p.: 243-247° C (dec).

EXAMPLE 34

Synthesis of 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine-5,5-dioxide

To a solution of 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine (20.0 g) in dichloromethane (250 ml) and methanol (250 ml) there was added 85% m-chloroperoxy benzoic acid (26.0 g) and the resulting mixture stirred at reflux temperature for 18 hours. After cooling, the insoluble solid was collected by filtration. It was suspended in 1,2-dichloroethane (250 ml) and ethanol (250 ml) and there was again added 85% m-chloroperoxybenzoic acid (1.35g). The mixture was refluxed for 18 hours, cooled and filtered to afford the title product (13.0g).
m.p.: 258-260° C.

Calc'd.	C: 44.87; H: 3.29; N: 3.27; S: 7.49
Found	C: 44.82; H: 3.21; N: 3.18; S: 7.67

EXAMPLE 35

Synthesis of 4-bromo-2,7-dimethoxy-3-hydroxy-10H-phenothiazine-5,5-dioxide

To a suspension of 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine-5,5-dioxide (10.0 g) in methanol (105 ml) there was added 2N aqueous sodium hydroxide solution (74 ml) and the resulting mixture was

stirred at room temperature for 20 minutes. There was then added 10% aqueous acetic acid solution (250 ml) and a thick precipitate was formed. The mixture was diluted with water (105 ml) and filtered, the solid washed with water and ether, and dried in a desiccator, affording the title compound (9.6 g). Further purification of a small sample was achieved through chromatography on a short column of silica gel, eluting with acetone. m.p.: 252-260° (dec).

EXAMPLE 36

Synthesis of 3-acetoxy-2,7-dimethoxy-10H-phenothiazine-5-oxide

The procedure of Example 33 was employed, substituting 3-acetoxy-2,7-dimethoxy-10H-phenothiazine for the 4-bromo analog, to afford the title compound.
m.p.: 238° C (dec).

EXAMPLE 37

Synthesis of 3-acetoxy-2,7-dimethoxy-10H-phenothiazine-5,5-dioxide

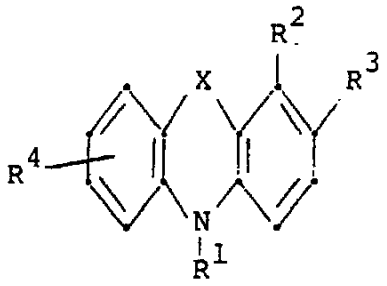
Following the procedure described in Example 34, but substituting 3-acetoxy-2,7-dimethoxy-10H-phenothiazine for the 4-bromo analog, there was obtained the title compound. m.p.: 265-268° C.

EXAMPLE 38

Synthesis of 2,7-dimethoxy-3-hydroxy-10H-phenothiazine-5,5-dioxide

Using the procedure described in example 35, but substituting 3-acetoxy-2,7-dimethoxy-10H-phenothiazine-5,5-dioxide for the 4-bromo analog, there was obtained the title compound. m.p.: 276-278° C (dec).

Following the procedures described above, the following compounds were prepared:



Example No.	X	R^1	R^2	R^3	R^4	m.p. (°C)
39	S	Me	Cl	OAc	H	132
40	S	Me	H	OMe	7-F	104
41	S	Ac	H	OMe	7-F	92
42	S	Ac	H	OH	7-F	195
43	S	Ac	H	OAc	7-F	144-145
44	S	Me	H	OMe	7-Me	102
45	S	H	H	OAc	7-F	175-176
46	S	Me	H	OMe	9-Cl	59
47	S	Me	H	OAc	9-Cl	87-88
48	S	Me	H	OAc	7-Me	108-110
49	S	H	H	OAc	9-Cl	117
50	S	H	CF_3	OAc	H	133
51	S	H	Cl	OTs	H	178
52	S	Ac	Cl	OMe	7-F	206
53	S	Ac	Cl	OH	7-F	209
54	S	Me	Cl	OMe	7-F	122
55	SO	H	H	OAc	H	220
56	SO_2	H	H	OAc	H	254-256
57	SO_2	H	Cl	OAc	H	274-277
58	SO_2	H	Cl	OH	H	286
59	SO_2	H	H	OH	7-F	>220
60	SO_2	H	H	OAc	7-F	222

Example No.	X	R^1	R^2	R^3	R^4	m.p. (°C)
61	SO_2	H	Cl	OTs	H	>240
62	SO_2	H	OH	OH	H	261
63	SO_2	H	OMe	OH	H	279

EXAMPLE 64

Synthesis of 4-chloro-2-ethoxy-3-hydroxy-10H-phenothiazine

By following the procedure described in Step 5 of Example 18, but substituting 4-chloro-2-ethoxy-3H-phenothiazin-3-one for 4-bromo-2,7-dimethoxy-3H-phenothiazin-3-one, the title compound was obtained, m.p. 186-189° C.

EXAMPLE 65

Synthesis of 1,2-dimethoxy-3-hydroxy-4-methyl-10H-phenothiazine, 5,5-dioxide

Starting with 1,2-dimethoxy-4-methyl-3H-phenothiazin-3-one, and using the procedures described in Step 5 of Example 18, Example 19, Example 34 and Example 26, the title compound was obtained, m.p. 218-220° C.

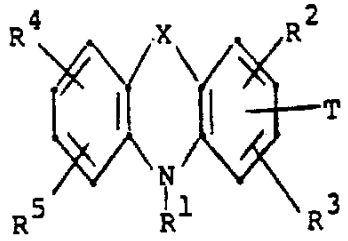
EXAMPLE 66

Synthesis of 4-Bromo-2,7-dimethoxy-3-hydroxy-10-(1-pivaloyloxyethoxycarbonyl)-10H-phenothiazine

Following the procedure of Example 29, Step 3, but substituting sodium pivaloate in place of mercuric acetate and pivalic acid in place of acetic acid, and heating at 85° for 4 hours, the title compound was obtained, m.p. 85°.

Claims

1. A pharmaceutical composition capable of inhibiting leukotriene biosynthesis or action in mammals and containing a pharmaceutical diluent, carrier or excipient and a compound of Formula I:



I

in which
X is Se, S, SO, SO_2 or O;
R^1 is H; C_{1-6} alkyl; acetyl; (C_{1-6} acyloxy)-(C_{1-6} alkyl); benzoyl; substituted benzoyl having C_{1-3} alkyl, halogen, CN, CF_3, $COOR^6$, CH_2COOR^6, $(CH_2)_nNR^8R^9$ (where n is 0, 1 or 2), C_{1-3} alkoxy, and/or OH substitution, (herein called "substituted as herein defined"); carbamoyl; $CO\text{-}NHR^7$; $COOR^7$; p-toluenesulfonyl; methanesulfonyl; an acyl group such that R^1-OH is an essential amino acid; benzyl;

phenethyl; $(CH_2)_pOR^a$ where R^a is C_{1-6} alkyl or phenyl and p is an integer from 1 to 5 when R^a is phenyl and is an integer from 1 to 6 when R^a is alkyl; $(CH_2)_nCOOR^6$ where n is 0, 1 or 2; or (C_{1-6} acyloxy)-(C_{1-6} alkoxy) carbonyl;

each of R^2, R^3, R^4 and R^5, independently of the others, is hydrogen; C_{1-6} alkyl; C_{2-6} alkenyl or $-(CH_2)_qM$ where q is 0 or an integer from 1 to 6 and M is (a) $-OR^{16}$; (b) halogen; (c) $-CF_3$; (d) $-SR^{16}$; (e) phenyl or substituted phenyl as herein defined; (f) $COOR^6$; (g) $-CO-R^{14}$; (h) tetrazolyl; (i) $-NH-CO-R^7$; (j) $-NR^8R^9$; (k) $-NHSO_2R^{10}$ where R^{10} is OH, C_{1-6} alkyl, C_{1-6} alkoxy or phenyl; (l) $-CO-CH_2OH$; (m) $-SOR^{11}$ where R^{11} is C_{1-6} alkyl, phenyl, substituted phenyl as herein defined, $(CH_2)_mCOOR^6$ where m is an integer from 1 to 6, CN, formyl, or C_{1-4} perfluoroalkyl; (n) $-CONR^8R^9$; (o) $-SO_2NR^8R^9$; (p) $-SO_2R^{13}$ where R^{13} is hydrogen, OH, C_{1-6} alkyl, phenyl, substituted phenyl as herein defined, $(CH_2)_mCOOR^6$ where m is as defined above, CN, formyl, or C_{1-4} perfluoroalkyl; (q) $-NO_2$; (r) $-O-CO-R^{14}$; (s) $O-CO-NR^8R^9$; or (t) -CN;

each R^6, independently of the others, is hydrogen, C_{1-6} alkyl or phenyl;

each R^7, independently of the others, is C_{1-6} alkyl, benzyl, phenyl or (C_{1-6} acyloxy)-(C_{1-6} alkyl);

each R^8 and each R^9, independently of any others, is hydrogen, C_{1-4} acyl, phenyl, or substituted phenyl as herein defined; or an R^8 and an R^9 are joined through the N to which they are both attached to form a heterocycloalkyl group having from 5 to 8 ring atoms;

each R^{14}, independently of the others, is hydrogen, $(CH_2)_rCOOR^6$ where r is 0 or an integer from 1 to 4; C_{1-6} alkyl; C_{1-6} alkoxy; (C_{1-6} acyloxy)(C_{1-6} alkoxy); phenyl; substituted phenyl as herein defined; or C_{1-6} aminoalkyl such that $R^{14}COOH$ is an essential amino acid;

each R^{15}, independently of any others, is hydrogen, (C_{1-5} alkoxy)-(C_{1-5} alkyl), C_{1-6} alkyl; benzyl; (C_{1-6} acyloxy)-(C_{1-6} alkyl); phenyl; substituted phenyl as herein defined; $-(CH_2)_mCOOR^6$ where m is as defined above; CN; formyl; perfluoroalkyl; or CH_2-R^{12} where R^{12} is C_{1-5} alkyl, dimethylamino or phenyl; and T is hydrogen or $-OR_{15}$, where R_{15} is hydrogen, C_{1-6} alkyl, (C_{1-6} alkyl)-acyl, phenylacyl, substituted phenyl-acyl as herein defined; benzoyl; substituted benzoyl as herein defined; or arylsulfonyl; and compounds that are pharmaceutically acceptable salts thereof.

2. A composition as claimed in Claim 1 in which, in the formula, X_1 is S, SO, SO_2 or O and the other substituents are as defined in Claim 1.

3. A composition as claimed in Claim 2 in which R^2, R^3, R^4 and R^5 are all other than C_{2-6} alkenyl.

4. A composition as claimed in Claim 3 in which, in the formula, X is S or O;

R^1 is H; C_{1-6} alkyl; C_{1-6} acyl; (C_{1-6} acyloxy)-(C_{1-6} alkyl); (C_{1-6} alkoxy)-(C_{1-6} alkyl); benzoyl; benzoyl substituted as herein defined; carbamoyl; $CO-NHR^7$; $COOR^7$; $(CH_2)_pOR^a$ where R^a is C_{1-6} alkyl or phenyl, and p is an integer from 1 to 5; $(CH_2)_nCOOR^6$ where n is 0, 1 or 2; or (C_{1-6} acyloxy)-(C_{1-6} alkoxy) carbonyl;

M, if included in R^2, R^3, R^4 or R^5 is (a) $-OR^{16}$; (b) halogen; (c) $-CF_3$; (d) $-SR^{16}$; (e) $COOR^6$; (f) $-NH-CO-R^7$; (g) $-NR^8R^9$; (h) $-SOR^{11}$ where R^{11} is C_{1-6} alkyl or C_{1-4} perfluoroalkyl; (i) $-SO_2R^{13}$ where R^{13} is C_{1-6} alkyl or C_{1-4} perfluoroalkyl; (j) $-O-CO-R^{14}$ where R_{14} is H, C_{1-6} alkyl, phenyl or substituted phenyl as herein defined; (k) $O-CO-NR^8R^9$; or (l) -CN;

each R^{16}, independently of the others, is hydrogen; C_{1-6} alkyl; benzyl; (C_{1-6} acyloxy)-(C_{1-6} alkyl) or C_{1-4} perfluoroalkyl;

T is hydrogen or $-OR_{15}$, where R_{15} is hydrogen, C_{1-6} alkyl, (C_{1-6} alkyl)-acyl, phenylacyl, substituted phenyl-acyl as herein defined, benzoyl or substituted benzoyl as herein defined; and the other variables are as defined in Claim 3.

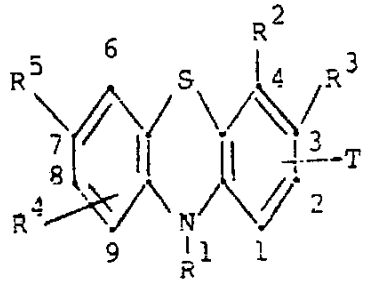
5. A composition as claimed in Claim 1 in which, in the formula

X is O or S,

R^1 is hydrogen, C_{1-4} alkyl, C_{1-4} alkylacyl, $(CH_2)_pOR^a$ where R^a is C_{1-4} alkyl or phenyl and p is 1, 2 or 3, (C_{1-4} acyloxy)-(C_{1-4} alkyl), (C_{1-4} alkoxy)carbonyl or (C_{1-4} acyloxy)-(C_{1-4} alkoxy)carbonyl;

each of R^2, R^3, R^4 and R^5, independently of the others, is hydrogen, halogen, hydroxyl; C_{1-3} alkyl; C_{1-3} alkoxy; C_{1-3} alkylthio; C_{1-5} acyloxy; benzoyloxy; C_{1-3} trihaloalkyl; C_{1-4} aminoalkyl; C_{1-5} acyl; $(CH_2)_mCOOR^6$, where m is 0, 1, 2, 3 or 4 and R^6 is H, phenyl or C_{1-6} alkyl; or (C_{1-4} acyloxy)-(C_{1-4} alkoxy)carbonyl; and T is as defined in Claim 1.

6. A composition as claimed in Claim 1 in which the compounds of Formula I are represented by Formula III:



III

in which
R^1 is H, C_{1-4} acyl, (C_{1-4} acyloxy)-(C_{1-4} alkyl), or C_{1-4} acyloxy)(C_{1-4} alkoxy)carbonyl;
R^2 is halogen;
R^3 is OH, C_{1-5} acyloxy, benzoyloxy, or (C_{1-4} acyloxy)-(C_{1-4} alkoxy)carbonyloxy;
R^4 is H, OH, C_{1-4} alkoxy or C_{1-4} acyloxy and is located at either position 1 or position 2;
R^5 is OH, C_{1-4} alkoxy or C_{1-4} acyloxy;
T is hydrogen or C_{1-4} alkoxy; or are pharmaceutically acceptable salts of such compounds.

7. A composition as claimed in Claim 1 in which, in the formula, the variables are as set forth in the following table:

Compound	X	R^1	R^2	R^3	R^4	R^5	T
1	S	H	H	H	H	H	H
2	S	Me	2-t-Bu	4-t-Bu	H	H	1-OH
3	S	Me	2-t-Bu	4-t-Bu	H	H	1-OMe
4	S	Me	2-t-Bu	4-t-Bu	H	H	1-OAc
5	S	Ac	2-t-Bu	4-t-Bu	H	H	1-OH
6	S	H	2-t-Bu	4-t-Bu	H	H	1-OMe
7	S	H	2-t-Bu	4-t-Bu	H	H	1-OAc
8	O	H	2-t-Bu	4-t-Bu	H	H	1-OH
9	S	CH_2OAc	2-t-Bu	4-t-Bu	H	H	1-OH
10	S	H	1-Cl	H	H	H	3-OH
11	S	H	1-Cl	H	H	H	3-OAc
12	S	H	1-Cl	H	H	H	3-OMe
13	S	Me	1-Cl	H	H	H	3-OH
14	S	Me	1-Cl	H	H	H	3-OAc
15	S	Me	1-Cl	H	H	H	3-OMe
16	S	CH_2OAc	1-Cl	H	H	H	3-OMe
17	S	CH_2OAc	1-Cl	H	H	H	3-OAc
18	O	H	1-Cl	H	H	H	3-OH
19	O	Me	1-Cl	H	H	H	3-OH
20	O	Me	1-Cl	H	H	H	3-OAc
21	O	Me	1-Cl	H	H	H	3-OMe

Compound	X	R^1	R^2	R^3	R^4	R^5	T
22	O	Ac	1-Cl	H	H	H	3-OAc
23	O	CH_2OAc	1-Cl	H	H	H	3-OMe
24	Se	Me	1-Cl	H	H	H	3-OMe
25	SO	H	1-Cl	H	H	H	3-OH
26	SO	H	1-Cl	H	H	H	3-OMe
27	SO	H	1-Cl	H	H	H	3-OAc
28	SO	Me	1-Cl	H	H	H	3-OH
29	SO	Me	1-Cl	H	H	H	3-OAc
30	SO	Me	1-Cl	H	H	H	3-OMe
31	SO_2	H	1-Cl	H	H	H	3-OH
32	SO_2	H	1-Cl	H	H	H	3-OAc
33	SO_2	H	1-Cl	H	H	H	3-OMe
34	SO_2	Me	1-Cl	H	H	H	3-OAc
35	SO_2	Me	1-Cl	7-OCH_2CO_2H	H	H	3-OAc
36	SO_2	Me	1-Cl	H	H	H	3-OMe
37	SO_2	Ac	1-Cl	H	H	H	3-OH
38	SO_2	Ac	1-Cl	H	H	H	3-OAc
39	SO_2	Ac	1-Cl	H	H	H	3-OMe
40	SO	Ac	1-Cl	H	H	H	3-OH
41	SO	Ac	1-Cl	H	H	H	3-OAc
42	SO	Ac	1-Cl	H	H	H	3-OMe
43	SO_2	CH_2OAc	1-Cl	H	H	H	3-OH
44	SO_2	CH_2OAc	1-Cl	H	H	H	3-OAc
45	SO_2	CH_2OAc	1-Cl	H	H	H	3-OMe
46	S	CH_2Ph	H	H	H	H	H
47	S	Me	H	H	H	H	H

Compound	X	R^1	R^2	R^3	R^4	R^5	T
48	S	Ac	H	H	H	H	H
49	S	CH_2OAc	H	H	H	H	H
50	O	H	H	H	H	H	H
51	O	Me	H	H	H	H	H
52	O	Ac	H	H	H	H	H
53	Se	H	H	H	H	H	H
54	Se	Me	H	H	H	H	H
55	Se	Ac	H	H	H	H	H
56	Se	CH_2OAc	H	H	H	H	H
57	SO	H	H	H	H	H	H
58	SO	Me	H	H	H	H	H
59	SO_2	Ac	H	H	H	H	H
60	S	H	H	H	H	H	3-OH
61	S	H	H	H	H	H	3-OAc
62	S	H	H	H	H	H	3-OMe
63	S	Me	H	H	H	H	3-OAc
64	S	Me	H	H	H	H	3-OH
65	S	Me	H	H	H	H	3-OMe
66	S	Ac	H	H	H	H	2-OH
67	S	Ac	H	H	H	H	3-OAc
68	S	Ac	H	H	H	H	3-OMe
69	S	CH_2OAc	H	H	H	H	3-OH
70	S	CH_2OAc	H	H	H	H	3-OAc
71	S	CH_2OAc	H	H	H	H	3-OMe
72	Same as compounds 60-71 but X=O						
73	Same as compounds 60-71 but X=Se						
74	S	H	4-Cl	H	H	H	3-OH
75	S	H	4-Cl	H	H	H	3-OMe
76	S	H	4-Cl	H	H	H	3-OAc

Compound	X	R^1	R^2	R^3	R^4	R^5	T
77	S	Me	4-Cl	H	H	H	3-OH
78	S	Me	4-Cl	H	H	H	3-OAc
79	S	Me	4-Cl	H	H	H	3-OMe
80	S	Ac	4-Cl	H	H	H	3-OH
81	S	Ac	4-Cl	H	H	H	3-OAc
82	S	Ac	4-Cl	H	H	H	3-OMe
83	S	Me	4-Cl	H	H	H	3-O-Bz
84	S	Me	4-Cl	H	H	H	3-OCOCH(Me)$_2$
85	S	Me	4-Cl	H	H	H	3-OCOC(Me)$_3$
86	SO_2	H	4-Cl	H	H	H	3-OH
87	SO_2	H	4-OH	H	H	H	3-OH
88	SO_2	H	4-Cl	H	H	H	3-OAc
89	SO_2	H	4-Cl	H	H	H	3-OMe
90	SO_2	Me	4-Cl	H	H	H	3-OH
91	SO_2	Me	4-Cl	H	H	H	3-OAc
92	SO_2	Me	4-Cl	H	H	H	3-OMe
93	SO_2	Ac	4-Cl	H	H	H	3-OH
94	SO_2	Ac	4-Cl	H	H	H	3-OAc
95	SO_2	Ac	4-Cl	H	H	H	3-OMe
96	S	CH_2OAc	4-Cl	H	H	H	H
97	S	CH_2OAc	4-Cl	H	H	H	3-OH
98	S	CH_2OAc	4-Cl	H	H	H	3-OAc
99	S	CH_2OAc	4-Cl	H	H	H	3-OMe
100	SO_2	CH_2OAc	4-Cl	H	H	H	3-OH
101	SO_2	CH_2OAc	4-Cl	H	H	H	3-OAc
102	SO_2	CH_2OAc	4-Cl	H	H	H	3-OMe
103	Same as compounds 74-103 but X=SO						
104	Same as compounds 74-103 but X=O						
105	Same as compounds 74-103 but R_4 is 7-Cl						

Compound	X	R^1	R^2	R^3	R^4	R^5	T
106	Same as compound 105 but X=O						
107	Same as compounds 74-103 but R_4 is 7-OMe						
108	Same as compound 107 but X=O						
109	Same as compounds 74-103 but R_4 is 7-(C_1-C_6 alkyl)						
110	Same as compound 109 but X=O						
111	Same as compounds 74-103 but R_4 is 7-(COMe)						
112	Same as compound 111 but X=O						
113	Same as compounds 74-103 but R_4 is 7-[$(CH_2)_m$COOR], wherein m is 0-4						
114	Same as compound 113 but X=O						
115	Same as compounds 74-103 but R_4 is 9-Cl						
116	S	H	4-Et	H	H	H	3-OH
117	S	Me	4-Et	H	H	H	3-O$COCH_2$Ph
118	S	Me	4-Et	H	H	H	3-OAc
119	S	Me	4-Et	H	H	H	3-OMe
120	S	H	4-OEt	H	H	H	3-OH
121	S	H	4-OEt	H	H	H	3-OMe
122	S	Me	4-OEt	H	H	H	3-OMe
123	S	Me	4-OEt	H	H	H	3-OAc
124	S	H	2-OEt	7-OEt	H	H	3-OH
125	S	H	2-OEt	7-OEt	H	H	3-OMe
126	S	Me	2-OEt	7-OEt	H	H	3-OMe
127	S	Me	2-OEt	7-OEt	H	H	3-OAc
128	S	H	H	H	H	H	3-OAc
129	S	Me	H	H	H	3-Ac	H
130	S	Ac	H	H	H	3-Ac	3-OAc
131	S	H	7-Ac	H	H	3-Ac	H
132	S	Me	7-Ac	H	H	3-Ac	H
133	S	Ac	7-Ac	H	H	3-Ac	H

Compound	X	R^1	R^2	R^3	R^4	R^5	T
134	S	CH_2OAc	7-Ac	H	H	3-Ac	H
135	S	H	2-Me	4-Cl	H	H	3-OH
136	S	Me	2-Me	4-Cl	H	H	3-OAc
137	S	H	7-Me	2-Me	H	H	3-OH
138	S	Me	7-Me	2-Me	H	H	3-OAc
139	S	H	2-OEt	4-Cl	H	H	3-OH
140	S	Me	2-OEt	4-Cl	H	H	3-OAc
141	S	H	2-S-n-Bu	4-Cl	H	H	3-OH
142	S	Me	2-S-n-Bu	4-Cl	H	H	3-OAc
143	S	Me	4-S-n-Bu	H	H	H	3-OAc
144	S	Me	2-O-Me	4-Br	H	H	3-OAc
145	S	Me	2-O-Me	4-Cl	H	H	3-OAc
146	S	Me	2-O-Me	4-Br	H	H	3-OH
147	S	H	2-O-Me	3-OH	H	H	7-OMe
148	S	H	1-OMe	3-OH	H	H	7-OMe
149	S	H	2-OMe	3-OH	1-Br	H	7-OMe
150	S	H	1-OMe	3-OH	2-Br	H	7-OMe
151	S	H	1-OMe	3-OH	4-Br	H	7-OMe
152	S	H	1-OMe	3-OH	2-Cl	H	7-OMe
153	S	H	1-OMe	3-OH	4-Cl	H	7-OMe
154	S	H	2-OMe	3-OH	1-Cl	H	7-OMe
155	S	H	2-OMe	3-OH	4-Cl	H	7-OMe
156	S	H	2-OEt	3-OH	1-Br	H	7-OEt
157	S	H	2-OEt	3-OH	4-Br	H	7-OEt
158	S	H	2-OEt	3-OH	1-Cl	H	7-OEt
159	S	H	2-OEt	3-OH	4-Cl	H	7-OEt
160	S	H	2-OMe	3-OH	1-Br	7-OMe	9-OMe
161	S	H	2-OMe	3-OH	4-Br	7-OMe	8-OMe

Compound	X	R^1	R^2	R^3	R^4	R^5	T
162	S	H	2-OMe	3-OH	4-F	H	7-OMe
163	S	H	2-OMe	3-OH	4-CF_3	H	7-OMe
164	S	H	2-OMe	3-OH	4-Br	H	7-OEt
165	S	H	2-OMe	3-OH	4-Cl	H	7-OEt
166	S	H	2-OMe	3-OH	4-F	H	7-OEt
167	S	H	2-OMe	3-OH	4-I	H	7-OMe
168	S	H	2-OMe	3-OH	4-CF_3	H	7-OEt
169	S	H	2-OEt	3-OH	4-Br	H	7-OMe
170	S	H	2-OEt	3-OH	4-Cl	H	7-OMe
171	S	H	2-OEt	3-OH	4-F	H	7-OMe
172	S	H	2-OEt	3-OH	4-CF_3	H	7-OMe
173	S	H	1-OMe	2-OMe	3-OH	4-Br	7-OMe
174	S	H	1-OMe	3-OH	H	H	2-OMe
175	S	H	1-OMe	3-OH	4-Br	H	2-OMe
176	Same as compounds 147-175 but X=O						
177	Same as compounds 147-175 but X=SO_2						
178	S	H	2-SMe	3-OH	4-Br	H	7-OMe
179	S	H	2-OMe	3-OH	4-Br	7-SMe	
180	SO_2	H	2-SO_2Me	3-OH	4-Br	H	7-OMe
181	Same as compounds 147-175 but X=SO						
182	S	H	4-Cl	H	H	H	3-OBz
183	S	H	4-Cl	H	H	H	3-OCOCH(Me)$_2$
184	S	Ac	H	H	7-F	H	3-OAc
185	S	Me	H	H	7-Me	H	3-OMe
186	S	H	H	H	7-F	H	3-OAc
187	S	Me	H	H	9-Cl	H	3-OMe
188	S	Me	H	H	9-Cl	H	3-OAc
189	S	Me	H	H	7-Me	H	3-OAc

Compound	X	R^1	R^2	R^3	R^4	R^5	T
190	S	H	H	H	9-Cl	H	3-OAc
191	S	H	H	4-CF_3	H	H	3-OAc
192	S	H	H	4-Cl	H	H	3-OTs
193	S	Ac	H	4-Cl	7-F	H	3-OMe
194	S	Ac	H	4-Cl	7-F	H	3-OH
195	S	Me	H	4-Cl	7-F	H	3-OMe
196	SO	H	H	H	H	H	3-OAc
197	SO_2	H	H	H	H	H	3-OAc
198	SO_2	H	H	H	H	H	3-OH
199	SO_2	H	H	H	7-F	H	3-OAc
200	SO_2	H	H	4-Cl	H	H	3-OTs
201	S	H	1-OMe	2-OMe	4-Me	H	3-OH
202	S	H	1-OMe	2-OMe	4-Me	H	3-OAc
203	SO_2	H	1-OMe	2-OMe	4-Me	H	3-OH
204	SO_2	H	4-OMe	H	H	H	3-OH
205	S	H	2-OMe	3-OH	4-Br	7-OMe	H
206	S	H	2-OMe	3-OAc	4-Br	7-OMe	H
207	S	H	2-OMe	3-OAc	4-Cl	7-OMe	H
208	SO_2	H	2-OMe	3-OH	4-Br	7-OMe	H
209	S	H	2-OMe	3-OAc	7-OMe	4-Br	H
210	S	H	2-OMe	3-OAc	7-OMe	4-Br	H
211	S	H	2-OMe	3-OBz	7-OMe	4-Br	H
212	S	Me	2-OMe	3-OMe	7-OMe	4-Br	H
213	S	H	2-OMe	3-OMe	7-OMe	4-Br	H
214	S	Ac	2-OMe	3-OAc	7-OMe	4-Br	H
215	S	Ac	2-OMe	3-OH	7-OMe	4-Br	H
216	S	Ac	2-OMe	3-OMe	7-OMe	4-Br	H
217	S	Me	2-OMe	3-OAc	7-OMe	4-Br	H

Compound	X	R^1	R^2	R^3	R^4	R^5	T
218	S	Me	2-OMe	3-OH	7-OMe	4-Br	H
219	SO_2	H	2-OMe	3-OH	7-OMe	4-Br	H
220	SO_2	H	2-OMe	3-OAc	7-OMe	4-Br	H
221	SO_2	H	2-OMe	3-OAc	7-OMe	4-Br	H
222	SO	H	2-OMe	3-OAc	7-OMe	4-Br	H
223	SO	H	2-OMe	3-OAc	7-OMe	4-Br	H
224	S	H	2-OMe	3-OCO_2Me	4-Br	7-OMe	H
225	S	H	2-OMe	3-OCO_2Et	4-Br	7-OMe	H
226	S	H	2-OMe	3-OCO_2CH(Me)OAc	4-Br	7-OMe	H
227	S	H	2-OMe	3-OCO_2CH(Me)OAc	4-Cl	7-OMe	H
228	S	CO_2Me	2-OMe	3-OH	4-Br	7-OMe	H
229	S	CO_2Et	2-OMe	3-OH	4-Br	7-OMe	H
230	S	CO_2CH(Me)OAc	2-OMe	3-OH	4-Br	7-OMe	H
231	S	CO_2CH(Me)OAc	2-OMe	3-OH	4-Cl	7-OMe	H
232	S	CO_2CH(Me)OAc	2-OMe	3-OH	4-F	7-OMe	H
233	S	CO_2CH(Me)OAc	2-OMe	3-OAc	4-Br	7-OMe	H
234	S	CO_2CH(Me)OAc	2-OMe	3-OCO_2CH(Me)OAc	4-Br	7-OMe	H
235	O	Ac	2-OMe	3-OH	4-Br	7-OMe	H
236	O	Ac	2-OMe	3-OAc	4-Br	7-OMe	H
237	O	CO_2CH(Me)OAc	2-OMe	3-OH	4-Br	7-OMe	H
238	O	CO_2CH(Me)OAc	2-OMe	3-OAc	4-Br	7-OMe	H
239	S	H	2-OMe	3-OH	4-Br	7-Me	H
240	S	H	2-OMe	3-OAc	4-Br	7-Me	H
241	S	H	2-OMe	3-OH	4-Br	7-F	H
242	S	H	2-OMe	3-OAc	4-Br	7-F	H

Compound	X	R^1	R^2	R^3	R^4	R^5	T
243	S	H	H	H	H	H	OCOEt
244	S	H	2-Cl	3-Cl	H	H	OCO-n-Pr
245	S	H	H	4-Cl	H	H	OCO-n-Bu
246	S	H	1-Me	H	H	H	H
247	S	H	2-CF_3	H	H	H	H
248	S	H	2-Et	H	H	H	H
249	S	H	H	3-Cl	7-OMe	H	H
250	S	H	H	3-Cl	7-Cl	H	H
251	S	H	H	3-NO_2	H	7-NO_2	H
252	S	H	3-NMe_2	H	H	7-NMe_2	H
253	S	H	1-OH	H	H	H	H
254	S	H	3-OAc	7-F	H	H	H
255	S	H	3-CH_2COMe	4-Cl	H	H	H
256	S	H	3-$OCOCHMe_2$	H	4-Cl	H	H
257	S	Ac	3-OMe	4-Cl	H	H	H
258	O	H	2-CF_3	H	H	H	H
259	S	Me	H	3-OMe	H	4-Cl	H
260	SO_2	H	4-Cl	3-OH	H	H	H
261	S	Me	7-F	4-Cl	3-OMe	H	H
262	S	Me	3-OMe	7-Me	H	H	H
263	S	Ac	4-Cl	H	H	H	H
264	S	Ac	3-OAc	4-Cl	H	H	H
265	SO_2	Ac	4-Cl	H	H	H	3-OH
266	SO_2	Ac	4-Cl	H	H	H	3 OAc
267	SO_2	Ac	4-Br	H	H	H	3-OAc

Compound	X	R^1	R^2	R^3	R^4	R^5	I
268	SO_2	$CO_2CH(Me)OAc$	4-Cl	H	H	H	3-OH
269	SO_2	H	4-Cl	H	H	$3-OCO_2CH(Me)OAc$	H
270	O	Ac	4-Cl	H	H	H	3-OAc
271	O	$CO_2CH(Me)OAc$	4-Cl	H	H	H	3-OH
272	O	$CO_2CH(Me)OAc$	4-Cl	H	H	H	3-OAc
273	O	H	4-Cl	H	H	$3-OCO_2CH(Me)OAc$	H
274	S	CH_2OAc	4-Cl	H	H	H	3-OAc
275	S	CH(Me)OAc	4-Cl	H	H	H	3-OAc
276	S	H	2-OMe	3-OH	7-OH	H	H
277	S	H	2-OMe	3-OH	7-OH	4-Br	H
278	S	H	2-OMe	3-OAc	7-OH	4-Br	H
279	S	H	2-OMe	3-OAc	7-OAc	4-Br	H

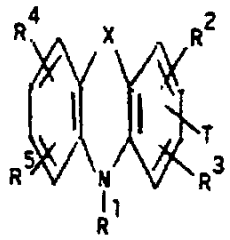
Compound	X	R^1	R^2	R^3	R^4	R^5	I
280	S	Ac	2-OMe	3-OH	7-OH	4-Br	H
281	S	Ac	2-OMe	3-OAc	7-OH	4-Br	H
282	S	Ac	2-OMe	3-OAc	7-OAc	4-Br	H
283	S	Ac	2-OMe	3-OH	7-OAc	4-Br	H
284	SO_2	Ac	2-OMe	3-OH	4-Br	7-OMe	H
285	SO_2	$CO_2CH(Me)OAc$	2-OMe	3-OAc	4-Br	7-OMe	H
286	SO_2	Ac	2-OMe	$3\text{-}OCO_2\overset{H}{\underset{Me}{C}}OAc$	4-Br	7-OMe	H
287	SO_2	Ac	2-OMe	3-OAc	4-Br	7-OMe	H
288	SO_2	$CO_2CH(Me)OAc$	2-OMe	3-OH	4-Br	7-OMe	H
289	S	Ac	2-OEt	3-OAc	4-Cl	H	H
290	S	Ac	2-OEt	3-OH	4-Cl	H	H
291	S	Me	H	7-Ac	H	H	3-OMe
292	S	Me	H	H	7-F	H	3-OMe
293	S	Ac	H	H	7-F	H	3-OMe
294	S	Ac	H	H	7-F	H	3-OH

8. A composition as claimed in Claim 7 in which the compound has one of the formulae numbered 13, 14, 31, 37, 38, 73, 76, 78, 79, 80, 81, 82, 84, 86, 87, 88, 92, 93, 94, 124, 139, 147, 151, 153, 155, 157, 159, 162, 163, 164, 165, 169, 170, 178, 179, 182 to 223 inclusive, 225 to 242 inclusive, 260 or 267 to 294 inclusive.

9. A composition as claimed in Claim 7 in which the compound has one of the formulae numbered 79, 80, 81, 86, 88, 93, 94, 197, 198, 214, 215, 226, 230, 233, 235, 236, 237, 275, 280, 283, 284, 287, 288, 289 and 290.

10. A composition as claimed in Claim 1 for use in (a) inhibiting mammalian leukotriene biosynthesis or action; (b) treating cardiovascular conditions; (c) treating inflammation; (d) treating allergies; (e) treating pain; (f) treating asthma; or (g) treating skin conditions.

11. Compounds having the formula:



I

in which the substituents are as set forth in the following table:

Compound	X	R^1	R^2	R^3	R^4	R^5	T
3	S	Me	4-Cl	H	H	H	3-OMe
8	S	Ac	4-Cl	H	H	H	3-OAc
9	S	Ac	4-Cl	H	H	H	3-OH

Compound	X	R^1	R^2	R^3	R^4	R^5	T
27	S	Ac	H	4-Cl	7-F	H	3-OMe
28	S	Ac	H	4-Cl	7-F	H	3-OH
29	S	Me	H	4-Cl	7-F	H	3-OMe
30	S	H	H	2-OEt	4-Cl	H	3-OH
32	SO_2	H	H	H	H	H	3-OAc
33	SO_2	H	H	4-Cl	H	H	3-OAc
34	SO_2	H	H	4-Cl	H	H	3-OH
39	S	H	1-OMe	2-OMe	4-Me	H	3-OH
40	S	H	1-OMe	2-OMe	4-Me	H	3-OAc
41	SO_2	H	1-OMe	2-OMe	4-Me	H	3-OH

Compound	X	R^1	R^2	R^3	R^4	R^5	I
43	S	H	1-OH	2-C(Me)$_3$	H	4-C(Me)$_3$	H
49	SO	H	1-OMe	2-OMe	4-Me	H	3-OH
50	SO	H	1-OMe	2-OMe	4-Me	H	3-OAc
51	SO_2	H	1-OMe	2-OMe	4-Me	H	3-OAc
52	S	H	2-OMe	3-OH	4-Br	7-OMe	H
53	S	H	2-OMe	3-OH	4-Cl	7-OMe	H
54	S	H	2-OMe	3-OAc	4-Br	7-OMe	H
55	S	H	2-OMe	3-OAc	4-Cl	7-OMe	H
56	SO_2	H	2-OMe	3-OH	4-Br	7-OMe	H
58	SO_2	H	2-OMe	3-OAc	4-Br	7-OMe	H
59	O	Ac	2-OMe	3-OH	4-Br	7-OMe	H
60	O	Ac	2-OMe	3-OAc	4-Br	7-OMe	H
61	O	CO_2CH(Me)OAc	2-OMe	3-OH	4-Br	7-OMe	H
62	O	CO_2CH(Me)OAc	2-OMe	3-OAc	4-Br	7-OMe	H
63	S	H	2-OMe	3-OH	4-Br	7-Me	H
64	S	H	2-OMe	3-OAc	4-Br	7-Me	H
65	S	H	2-OMe	3-OH	4-Br	7-F	H
66	S	H	2-OMe	3-OAc	4-Br	7-F	H
67	SO	H	2-OMe	3-OAc	4-Br	7-OMe	H
68	SO_2	H	2-OMe	3-OH	H	7-OMe	H
69	SO_2	H	2-OMe	3-OAc	H	7-OMe	H
70	S	Ac	2-OMe	4-Br	7-OMe	H	3-OAc

Compound	X	R^1	R^2	R^3	R^4	R^5	I
71	S	Ac	2-OMe	4-Cl	7-OMe	H	3-OAc
72	S	Ac	2-OMe	4-F	7-OMe	H	3-OAc
73	S	Ac	2-OMe	4-I	7-OMe	H	3-OAc
74	S	Ac	2-OMe	4-CF_3	7-OMe	H	3-OAc
75	S	Ac	2-OMe	4-CN	7-OMe	H	3-OAc
76	S	Ac	2-OEt	4-Br	7-OEt	H	3-OAc
77	S	Ac	2-OEt	4-Cl	7-OEt	H	3-OAc
78	S	Ac	2-OMe	4-Br	7-OEt	H	3-OAc
79	S	Ac	2-OMe	4-Cl	7-OEt	H	3-OAc
80	S	Ac	2-OMe	4-F	7-OEt	H	3-OAc
81	S	Ac	2-OEt	4-Br	7-OMe	H	3-OAc
82	S	Ac	2-OEt	4-Cl	7-OMe	H	3-OAc
83	S	Ac	2-OEt	4-F	7-OMe	H	3-OAc
84	S	Ac	2-OEt	4-CF_3	7-OMe	H	3-OAc
85	S	H	2-OMe	4-Br	7-OMe	H	3-OH
86	S	H	2-OMe	4-Cl	7-OMe	H	3-OH
87	S	H	2-OMe	4-F	7-OMe	H	3-OH
88	S	H	2-OMe	4-CF_3	7-OMe	H	3-OH
89	S	H	2-OMe	4-Br	7-OMe	H	3-OAc
90	S	H	2-OMe	4-Br	7-OMe	H	3-OBz
91	S	H	2-OMe	4-Br	7-OMe	H	3-OCOCHMe$_2$
92	S	H	2-OMe	4-Br	7-OMe	3-OCH_2CO_2H	H
93	S	Ac	2-OMe	4-Br	7-OMe	H	3-OBz
94	S	Ac	2-OMe	4-Br	7-OMe	H	3-OMe
95	S	Ac	2-OMe	4-Br	7-OMe	3-OCH_2CO_2H	H
96	S	Ac	2-OMe	4-Cl	7-OMe	3-OCH_2CO_2H	H
97	S	CH_2OAc	2-OMe	4-Br	7-OMe	H	3-OH
98	S	CH_2OAc	2-OMe	4-Cl	7-OMe	H	3-OH
99	S	CH_2OAc	2-OMe	4-Br	7-OMe	H	3-OAc

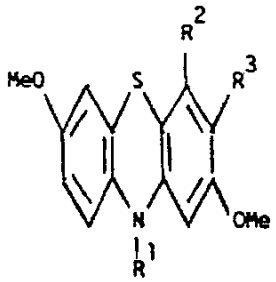
Compound	X	R^1	R^2	R^3	R^4	R^5	T
100	S	CH_2OAc	2-OMe	4-Br	7-OMe	H	3-OBz
101	S	CH_2OAc	2-OMe	4-Br	7-OMe	H	3-OMe
102	S	CH_3	2-OMe	4-Br	7-OMe	H	3-OH
103	S	CH_3	2-OMe	4-Br	7-OMe	H	3-OAc
104	S	CH_3	2-OMe	4-Cl	7-OMe	H	3-OH
105	S	Me	2-OMe	4-F	7-OMe	H	3-OH
106	S	Me	2-OMe	4-CF_3	7-OMe	H	3-OH
107	S	CH(Me)OAc	2-OMe	4-Br	7-OMe	H	3-OH
108	S	$CH(Me)OCOC(Me)_3$	2-OMe	4-Br	7-OMe	H	3-OH
109	S	CH(Me)OAc	2-OMe	4-Cl	7-OMe	H	3-OH
110	S	CH(Me)OAc	2-OMe	4-F	7-OMe	H	3-OH
111	S	CH(Me)OAc	2-OMe	4-CF_3	7-OMe	H	3-OH
112	S	H	2-OMe	4-Br	7-OMe	3-OCO_2Me	H
113	S	H	2-OMe	4-Br	7-OMe	3-OCO_2Et	H
114	S	H	2-OMe	4-Br	7-OMe	3-$OCO_2CH(Me)OAc$	H
115	S	H	2-OMe	4-Cl	7-OMe	3-$OCO_2CH(Me)OAc$	H
116	S	CO_2Me	2-OMe	4-Br	7-OMe	H	3-OH
117	S	CO_2Et	2-OMe	4-Br	7-OMe	H	3-OH
118	S	$CO_2CH(Me)OAc$	2-OMe	4-Br	7-OMe	H	3-OH
119	S	$CO_2CH(Me)OAc$	2-OMe	4-Cl	7-OMe	H	3-OH
120	S	$CO_2CH(Me)OAc$	2-OMe	4-F	7-OMe	H	3-OH
121	S	$CO_2CH(Me)OAc$	2-OMe	4-Br	7-OMe	H	3-OAc
122	S	$CO_2CH(Me)OAc$	2-OMe	4-Br	7-OMe	3-$OCO_2CH(Me)OAc$	H
123	S	Ac	2-OMe	4-Br	7-OMe	H	3-OH
124	S	Ac	2-OMe	4-Cl	7-OMe	H	3-OH
125	S	Me	2-OMe	4-Br	7-OMe	H	3-OMe
126	S	H	2-OMe	4-Br	7-OMe	H	3-OMe
127	S	CH(Me)OAc	4-Cl	H	H	H	3-OAc
128	SO_2	Ac	4-Cl	H	H	H	3-OH

Compound	X	R^1	R^2	R^3	R^4	R^5	I
129	SO_2	Ac	4-Cl	H	H	H	3-OAc
130	S	Ac	2-OEt	4-Cl	H	H	3-OH
131	S	Ac	2-OEt	4-Cl	H	H	3-OAc
132	S	Ac	2-OMe	4-Br	7-OH	H	3-OH
133	S	Ac	2-OMe	4-Br	7-OAc	H	3-OH
134	SO_2	Ac	2-OMe	4-Br	7-OMe	H	3-OH
135	SO_2	Ac	2-OMe	4-Br	7-OMe	H	3-OAc
136	SO_2	$CO_2CH(Me)OAc$	2-OMe	4-Br	7-OMe	H	3-OH
137	S	CO_2CHOCO (Me, $C(Me)_3$)	H	4-Br	7-OMe	2-OMe	3-OH
138	S	H	2-OMe	4-I	7-OMe	H	3-OH
139	S	H	2-OMe	4-CN	7-OMe	H	3-OH
140	S	H	2-OEt	4-Br	7-OEt	H	3-OH
141	S	H	2-OEt	4-Cl	7-OEt	H	3-OH
142	S	H	2-OMe	4-Br	7-OEt	H	3-OH
143	S	H	2-OMe	4-Cl	7-OEt	H	3-OH
144	S	H	2-OMe	4-F	7-OEt	H	3-OH
145	S	H	2-OEt	4-Br	7-OMe	H	3-OH
146	S	H	2-OEt	4-Cl	7-OMe	H	3-OH
147	S	H	2-OEt	4-F	7-OMe	H	3-OH
148	S	H	2-OEt	4-CF_3	7-OMe	H	3-OH

12. The compounds having variables in Formula I as numbered 3, 8, 9, 32, 33, 34, 41, 59, 60, 61, 70, 71, 114, 118, 119, 121, 123 or 127 to 137 inclusive in Claim 11.

13. The compounds having variables in Formula I as numbered 70, 71, 118, 119, 121, 123 or 137 in Claim 11.

14. Compounds according to Claim 11 having the formula:

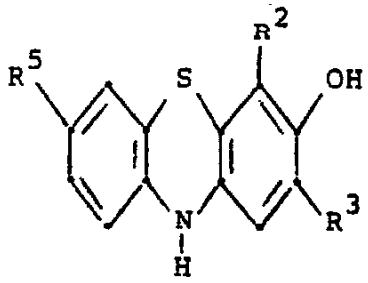


in which the substituents are as set forth in the following table:

R^1	R^2	R^3
H	Br	OH
H	Cl	OH
H	F	OH
H	CF_3	OH
H	Br	OAc
H	Br	OCOPh

R^1	R^2	R^3
H	Br	$OCOCHMe_2$
H	Br	OCH_2CO_2H
Ac	Br	OAc
Ac	Cl	OAc
Ac	Br	OCOPh
Ac	Br	OMe
Ac	Br	OCH_2CO_2H
Ac	Cl	OCH_2CO_2H
CH_2OAc	Br	OH
CH_2OAc	Cl	OH
CH_2OAc	Br	OAc
CH_2OAc	Br	OCOPh
CH_2OAc	Br	OMe
CH_3	Br	OH
CH_3	Br	OAc
CH_3	Cl	OH
CH_3	F	OH
CH_3	CF_3	OH
$CH(CH_3)OAc$	Br	OH
$CH(CH_3)OCOC(CH_3)_3$	Br	OH
$CH(CH_3)OAc$	Cl	OH
$CH(CH_3)OAc$	F	OH
$CH(CH_3)OAc$	CF_3	OH
$CO_2CH(Me)OAc$	Br	OH
$CO_2CH(Me)OAc$	Br	OAc

15. Compounds according to Claim 11 having the formula:



in which the substituents are as set forth in the following table:

R^2	R^3	R^5
Br	OMe	OMe
Cl	OMe	OMe
F	OMe	OMe
I	OMe	OMe
CF_3	OMe	OMe
CN	OMe	OMe
Br	OEt	OEt
Cl	OEt	OEt
Br	OMe	OEt
Cl	OMe	OEt
F	OMe	OEt
Br	OEt	OMe
Cl	OEt	OMe
F	OEt	OMe
CF_3	OEt	OMe

16. 3-Acetoxy-10-acetyl-4-bromo-2,7-dimethoxy-10H-phenothiazine.

17. 10-(1-Acetoxyethoxycarbonyl)-4-bromo-2,7-dimethoxy-3-hydyroxy-10H-phenothiazine.

18. 3-Acetoxy-10-acetyl-4-chloro-2,7-dimethoxy-10H-phenothiazine.

19. 4-Bromo-2,7-dimethoxy-3-hydroxy-10-(1-pivaloyloxyethoxycarbonyl)-10H-phenothiazine.

20. 3-Hydroxy-10-(1-acetoxyethoxycarbonyl)-4-chloro-2,7-dimethoxy-10H-phenothiazine.

21. 3-Acetoxy-10-(1-acetoxyethoxycarbonyl)-4-bromo-2,7-dimethoxy-10H-phenothiazine.

22. 3-Hydroxy-10-acetyl-4-bromo-2,7-dimethoxy-10H-phenothiazine.

23. A composition as claimed in any one of Claims 1 to 9 additionally comprising an effective amount of a second active ingredient that is a non-steroidal anti-inflammatory drug; a peripheral analgesic agent; a cyclooxygenase inhibitor; a leukotriene antagonist; a leukotriene inhibitor; an H_2-receptor antagonist; an antihistaminic agent; a prostaglandin antagonist or a thromboxane antagonist.

24. A composition as claimed in Claim 23 in which the weight ratio of the compound of Formula I to the second active ingredient is in the range from 1000:1 to 1:1000.

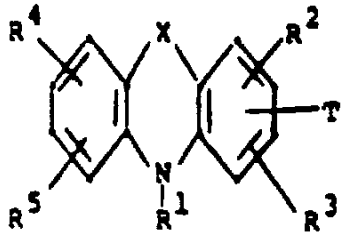
25. A composition as claimed in Claim 24 in which the aid ratio is from 200:1 to 1:200.

26. A composition according to any one of Claims 23 to 25 in which the second active ingredient is a non-steroidal anti-inflammatory drug.

27. A composition according to Claim 26 in which the non-steroidal anti-inflammatory drug is indomethacin.

Revendications

1. Composition pharmaceutique capable d'inhiber la biosynthèse ou l'action des leucotriènes chez les mammifères et contenant un diluant, véhicule ou excipient pharmaceutique et un composé de formule générale I :



I

dans laquelle
X est Se, S, SO, SO_2 ou O;
R^1 est H; un groupe alkyle en C_1-C_6; acétyle; (acyloxy en C_1-C_6)-(alkyle en C_1-C_5); benzoyle; benzoyle substitué comportant une substitution alkyle en C_1-C_3, halogène, CN, CF_3, $COOR^6$, CH_2COOR^6, $(CH_2)_nNR^8R^9$ (où n est égal à 0, 1 ou 2), alcoxy en C_1-C_3 et/ou OH (que l'on qualifie ici de "substitué tel que défini ici"); carbamoyle; $CO\text{-}NHR^7$; $COOR^7$; p-toluènesulfonyle; méthanesulfonyle; un groupe acyle tel que R^1-OH soit un acide aminé essentiel; benzyle; phénéthyle; $(CH_2)_pOR^a$, où R^a est un groupe alkyle en C_1-C_6 ou phényle et p est un nombre entier de 1 à 5, lorsque R^a est un groupe phényle, et est un nombre entier de 1 à 6, lorsque R^a est un groupe alkyle; $(CH_2)_nCOOR^6$, dans lequel n est égal à 0, 1 ou 2; ou (alcylxy en C_1-C_6)-(alcoxy en C_1-C_6)carbonyle;
chacun des radicaux R^2, R^3, R^4 et R^5, indépendamment des autres, est un hydrogène; un groupe alkyle en C_1-C_6; alcényle en C_2-C_6 ou $-(CH_2)_qM$, où q est nul ou un nombre entier de 1 à 6 et M est (a) $-OR^{16}$; (b) un halogène; (c) $-CF_3$; (d) $-SR^{16}$; (e) un groupe phényle ou phényle substitué tel que défini ici; (f) $COOR^6$; (g) $-CO\text{-}R^{14}$; (h) un groupe tétrazolyle; (i) $-NH\text{-}CO\text{-}R^7$; (j) $-NR^8R^9$; (k) $-NHSO_2R^{10}$, ou R^{10} est OH, un groupe alkyle en C_1-C_6, alcoxy en C_1-C_5 ou phényle; (1) $-CO\text{-}CH_2OH$; (m) $-SOR^{11}$, où R^{11} est un groupe alkyle en C_1-C_6, phényle, phényle substitué tel que défini ici, $(CH_2)_mCOOR^6$, où m est un nombre entier de 1 à 6, CN, un groupe formyle ou perfluoroalkyle en C_1-C_4; (n) $-CONR^8R^9$; (o) $-SO_2NR^8R^9$; (p) $-SO_2R^{13}$, où R^{13} est un hydrogène, OH, un groupe alkyle en C_1-C_6, phényle, phényle substitué tel que défini ici, $(CH_2)_mCOOR^6$, dans lequel m est tel que défini ci-dessus, CN, formyle ou perfluoroalkyle en C_1-C_4; (q) $-NO_2$; (r) $-O\text{-}CO\text{-}R^{14}$; (s) $O\text{-}CO\text{-}NR^8R^9$; ou (t) -CN;
chaque R^6, indépendamment des autres, est un hydrogène, un groupe alkyle en C_1-C_6 ou phényle;
chaque R^7, indépendamment des autres, est un groupe alkyle en C_1-C_6, benzyle, phényle ou (acyloxy en C_1-C_6)-(alkyle en C_1-C_6);
chaque R^8 et chaque R^9, indépendamment des autres, est un hydrogène, un groupe acyle en C_1-C_4, phényle ou phényle substitué tel que défini ici; ou un radical R^8 et un radical R^9 sont liés par

l'intermédiaire du N auquel ils sont tous deux fixés pour former un groupe hétérocycloalkylique comportant 5 à 8 atomes dans le noyau;
chaque R^{14}, indépendamment des autres, est un hydrogène, un groupe $(CH_2)_rCOOR^6$, dans lequel r est nul ou un nombre entier de 1 à 4; un groupe alkyle en C_1-C_6; alcoxy en C_1-C_6; (acyloxy en C_1-C_6)-(alcoxy en C_1-C_6); phényle; phényle substitué tel que défini ici; ou aminoalkyle en C_1-C_6 tel que $R^{14}COOH$ soit un acide aminé essentiel;
chaque R^{16}, indépendamment des autres, est un hydrogène, un groupe (alcoxy en C_1-C_5)-(alkyle en C_1-C_5), alkyle en C_1-C_6; benzyle; (acyloxy en C_1-C_6)-(alkyle en C_1-C_6); phényle; phényle substitué tel que défini ici; $(CH_2)_mCOOR^6$, où m est tel que défini ci-dessus; CN; formyle; perfluoroalkyle; ou CH_2-R^{12}, dans lequel R^{12} est un groupe alkyle en C_1-C_5, diméthylamino ou phényle;
et T est un hydrogène ou un groupe -OR^{15}, dans lequel R^{15} est un hydrogène, un groupe alkyle en C_1-C_6, (alkyl en C_1-C_6)-acyle, phénylacyle, (phényl substitué)-acyle tel que défini ci-dessus; benzoyle; benzoyle substitué tel que défini ci-dessus; ou arylsulfonyle; et les composés qui sont leurs sels pharmaceutiquement acceptables.

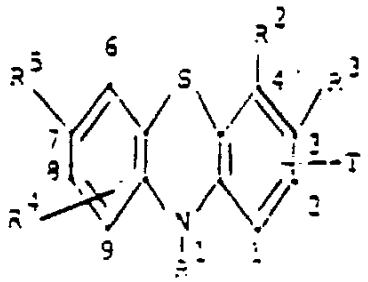
2. Composition selon la revendication 1, dans laquelle, dans la formule, X_1 est S, SO, SO_2 ou O, et les autres substituants sont tels que définis dans la revendication 1.

3. Composition selon la revendication 2, dans laquelle R^2, R^3, R^4 et R^5 sont tous différents d'un groupe alcényle en C_2-C_6.

4. Composition selon la revendication 3, dans laquelle, dans la formule, X est S ou O;
R^1 est H; un groupe alkyle en C_1-C_6; acyle en C_1-C_6; (acyloxy en C_1-C_6)-(alkyle en C_1-C_6); (alcoxy en C_1-C_6)-(alkyle en C_1-C_6); benzoyle; benzoyle substitué tel que défini ici; carbamoyle; CO-NHR^7; $COOR^7$; $(CH_2)_pOR^a$, dans lequel R^a est un groupe alkyle en C_1-C_6 ou phényle, et p est un nombre entier de 1 à 5; $(CH_2)_nCOOR^6$, dans lequel n est égal à 0, 1 ou 2; ou (acyloxy en C_1-C_6)-(alcoxy en C_1-C_6)carbonyle;
M, s'il est inclus dans R^2, R^3, R^4 ou R^5, est (a) -OR^{15}; (b) un halogène; (c) -CF_3; (d) -SR^{15}; (e) $COOR^5$; (f) -NH-CO-R^7; (g) -NR^8R^9; (h) -SOR^{11}, dans lequel R^{11} est un groupe alkyle en C_1-C_6 ou perfluoroalkyle en C_1-C_4; (i) -SO_2R^{13}, dans lequel R^{13} est un groupe alkyle en C_1-C_6 ou perfluoroalkyle en C_1-C_4; (j) -O-CO-R^{14}, dans lequel R^{14} est H, un groupe alkyle en C_1-C_6, phényle ou phényle substitué tel que défini ici; (k) O-CO-NR^8R^9; ou (1) -CN;
chaque R^{16}, indépendamment des autres, est un hydrogène; un groupe alkyle en C_1-C_6; benzyle; (acyloxy en C_1-C_6)-(alkyle en C_1-C_6) ou perfluoroalkyle en C_1-C_4;
T est un hydrogène ou un groupe -OR^{15}, dans lequel R^{15} est un hydrogène, un groupe alkyle en C_1-C_6, (alkyl en C_1-C_6)acyle, phénylacyle, (phényl substitué)-acyle tel que défini ici, benzoyle ou benzoyle substitué tel que défini ici;
et les autres variables sont telles que définies dans la revendication 3.

5. Composition selon la revendication 1, dans laquelle, dans la formule,
X est O ou S,
R^1 est un hydrogène, un groupe alkyle en C_1-C_4, alkylacyle en C_1-C_4, -$(CH_2)_pOR^a$, dans lequel R^a est un groupe alkyle en C_1-C_4 ou phényle et p est égal à 1, 2 ou 3, (acyloxy en C_1-C_4)-(alkyle en C_1-C_4), (alcoxy en C_1-C_4)carbonyle ou (acyloxy en C_1-C_4)-(alcoxy en C_1-C_4)carbonyle;
chacun des radicaux R^2, R^3, R^4 et R^5, indépendamment des autres, est un hydrogène, un halogène, un hydroxyle; un groupe alkyle en C_1-C_3; alcoxy en C_1-C_3; alkylthio en C_1-C_3; acyloxy en C_1-C_5; benzoyloxy; trihalogénoalkyle en C_1-C_3; aminoalkyle en C_1-C_4; acyle en C_1-C_5; $(CH_2)_mCOOR^6$, dans lequel m est égal à 0, 1, 2, 3 ou 4 et R^6 est H, un groupe phényle ou alkyle en C_1-C_6; ou un groupe (acyloxy en C_1-C_4)-(alcoxy en C_1-C_4)carbonyle; et T est tel que défini dans la revendication 1.

6. Composition selon la revendication 1, dans laquelle les composés de formule I sont représentés par la formule III :



III

dans laquelle
R^1 est H, un groupe acyle en C_1-C_4, (acyloxy en C_1-C_4)-(alkyle en C_1-C_4) ou (acyloxy en C_1-C_4)-(alcoxy en C_1-C_4)-carbonyle;
R^2 est un halogène;
R^3 est OH, un groupe acyloxy en C_1-C_5, benzoyloxy ou (acyloxy en C_1-C_4)-(alcoxy en C_1-C_4)-carbonyloxy;
R^4 est H, OH, un groupe alcoxy en C_1-C_4 ou acyloxy en C_1-C_4 et est situé en position 1 ou en position 2;
R^5 est OH, un groupe alcoxy en C_1-C_4 ou acyloxy en C_1-C_4;
T est un hydrogène ou un groupe alcoxy en C_1-C_4; ou sont les sels pharmaceutiquement acceptables de ces composes.

7. Composition selon la revendication 1, dans laquelle, dans la formule, les variables sont telles que définies dans le tableau suivant :

Composé	X	R^1	R^2	R^3	R^4	R^5	T
1	S	H	H	H	H	H	H
2	S	Me	2-t-Bu	4-t-Bu	H	H	1-OH
3	S	Me	2-t-Bu	4-t-Bu	H	H	1-OMe
4	S	Me	2-t-Bu	4-t-Bu	H	H	1-OAc
5	S	Ac	2-t-Bu	4-t-Bu	H	H	1-OH
6	S	H	2-t-Bu	4-t-Bu	H	H	1-OMe
7	S	H	2-t-Bu	4-t-Bu	H	H	1-OAc
8	O	H	2-t-Bu	4-t-Bu	H	H	1-OH
9	S	CH_2OAc	2-t-Bu	4-t-Bu	H	H	1-OH
10	S	H	1-Cl	H	H	H	3-OH
11	S	H	1-Cl	H	H	H	3-OAc
12	S	H	1-Cl	H	H	H	3-OMe
13	S	Me	1-Cl	H	H	H	3-OH
14	S	Me	1-Cl	H	H	H	3-OAc
15	S	Me	1-Cl	H	H	H	3-OMe
16	S	CH_2OAc	1-Cl	H	H	H	3-OMe
17	S	CH_2OAc	1-Cl	H	H	H	3-OAc
18	O	H	1-Cl	H	H	H	3-OH
19	O	Me	1-Cl	H	H	H	3-OH
20	O	Me	1-Cl	H	H	H	3-OAc
21	O	Me	1-Cl	H	H	H	3-OMe

Composé	X	R^1	R^2	R^3	R^4	R^5	Y
22	O	Ac	1-Cl	H	H	H	3-OAc
23	O	CH_2OAc	1-Cl	H	H	H	3-OMe
24	Se	Me	1-Cl	H	H	H	3-OMe
25	SO	H	1-Cl	H	H	H	3-OH
26	SO	H	1-Cl	H	H	H	3-OMe
27	SO	H	1-Cl	H	H	H	3-OAc
28	SO	Me	1-Cl	H	H	H	3-OH
29	SO	Me	1-Cl	H	H	H	3-OAc
30	SO	Me	1-Cl	H	H	H	3-OMe
31	SO_2	H	1-Cl	H	H	H	3-OH
32	SO_2	H	1-Cl	H	H	H	3-OAc
33	SO_2	H	1-Cl	H	H	H	3-OMe
34	SO_2	Me	1-Cl	H	H	H	3-OAc
35	SO_2	Me	1-Cl	7-OCH_2CO_2H	H	H	3-OAc
36	SO_2	Me	1-Cl	H	H	H	3-OAc
37	SO_2	Ac	1-Cl	H	H	H	3-OH
38	SO_2	Ac	1-Cl	H	H	H	3-OAc
39	SO_2	Ac	1-Cl	H	H	H	3-OMe
40	SO	Ac	1-Cl	H	H	H	3-OH
41	SO	Ac	1-Cl	H	H	H	3-OAc
42	SO	Ac	1-Cl	H	H	H	3-OAc
43	SO_2	CH_2OAc	1-Cl	H	H	H	3-OH
44	SO_2	CH_2OAc	1-Cl	H	H	H	3-OAc
45	SO_2	CH_2OAc	1-Cl	H	H	H	3-OMe
46	S	CH_2Ph	H	H	H	H	H
47	S	Me	H	H	H	H	H

Composé	X	R^1	R^2	R^3	R^4	R^5	T
48	S	Ac	H	H	H	H	H
49	S	CH_2OAc	H	H	H	H	H
50	O	H	H	H	H	H	H
51	O	Me	H	H	H	H	H
52	O	Ac	H	H	H	H	H
53	Se	H	H	H	H	H	H
54	Se	Me	H	H	H	H	H
55	Se	Ac	H	H	H	H	H
56	Se	CH_2OAc	H	H	H	H	H
57	SO	H	H	H	H	H	H
58	SO	Me	H	H	H	H	H
59	SO_2	Ac	H	H	H	H	H
60	S	H	H	H	H	H	3-OH
61	S	H	H	H	H	H	3-OAc
62	S	H	H	H	H	H	3-OMe
63	S	Me	H	H	H	H	3-OAc
64	S	Me	H	H	H	H	3-OH
65	S	Me	H	H	H	H	3-OMe
66	S	Ac	H	H	H	H	2-OH
67	S	Ac	H	H	H	H	3-OAc
68	S	Ac	H	H	H	H	3-OMe
69	S	CH_2OAc	H	H	H	H	3-OH
70	S	CH_2OAc	H	H	H	H	3-OAc
71	S	CH_2OAc	H	H	H	H	3-OMe
72	Identique aux composés 60-71 mais X=O						
73	Identique aux composés 60-71 mais X=Se						
74	S	H	4-Cl	H	H	H	3-OH
75	S	H	4-Cl	H	H	H	3-OMe
76	S	H	4-Cl	H	H	H	3-OAc

Composé	X	R^1	R^2	R^3	R^4	R^5	T
77	S	Me	4-Cl	H	H	H	3-OH
78	S	Me	4-Cl	H	H	H	3-OAc
79	S	Me	4-Cl	H	H	H	3-OMe
80	S	Ac	4-Cl	H	H	H	3-OH
81	S	Ac	4-Cl	H	H	H	3-OAc
82	S	Ac	4-Cl	H	H	H	3-OMe
83	S	Me	4-Cl	H	H	H	3-O-Bz
84	S	Me	4-Cl	H	H	H	3-OCOCH(Me)_2
85	S	Me	4-Cl	H	H	H	3-OCOC(Me)_3
86	SO_2	H	4-Cl	H	H	H	3-OH
87	SO_2	H	4-OH	H	H	H	3-OH
88	SO_2	H	4-Cl	H	H	H	3-OAc
89	SO_2	H	4-Cl	H	H	H	3-OMe
90	SO_2	Me	4-Cl	H	H	H	3-OH
91	SO_2	Me	4-Cl	H	H	H	3-OAc
92	SO_2	Me	4-Cl	H	H	H	3-OMe
93	SO_2	Ac	4-Cl	H	H	H	3-OH
94	SO_2	Ac	4-Cl	H	H	H	3-OAc
95	SO_2	Ac	4-Cl	H	H	H	3-OMe
96	S	CH_2OAc	4-Cl	H	H	H	H
97	S	CH_2OAc	4-Cl	H	H	H	3-OH
98	S	CH_2OAc	4-Cl	H	H	H	3-OAc
99	S	CH_2OAc	4-Cl	H	H	H	3-OMe
100	SO_2	CH_2OAc	4-Cl	H	H	H	3-OH
101	SO_2	CH_2OAc	4-Cl	H	H	H	3-OAc
102	SO_2	CH_2OAc	4-Cl	H	H	H	3-OMe
103	Identique aux composés 74-103 mais X=SO						
104	Identique aux composés 74-103 mais X=O						
105	Identique aux composés 74-103 mais R_4 est 7-Cl						

Composé	X	R^1	R^2	R^3	R^4	R^5	T
106	Identique au composé 105 mais X=O						
107	Identique aux composés 74-103 mais R_4 est 7-OMe						
108	Identique au composé 107 mais X=O						
109	Identique aux composés 74-103 mais R_4 est 7-(C_1-C_6 alkyl)						
110	Identique au composé 109 mais X=O						
111	Identique aux composés 74-103 mais R_4 est 7-(COMe)						
112	Identique au composé 111 mais X=O						
113	Identique aux composés 74-103 mais R_4 est 7-($(CH_2)_m$COOR), où m est 0-4						
114	Identique au composé 113 mais X=O						
115	Identique aux composé 74-103 mais R_4 est 9-Cl						
116	S	H	4-Et	H	H	H	3-OH
117	S	Me	4-Et	H	H	H	3-$OCOCH_2Ph$
118	S	Me	4-Et	H	H	H	3-OAc
119	S	Me	4-Et	H	H	H	3-OMe
120	S	H	4-OEt	H	H	H	3-OH
121	S	H	4-OEt	H	H	H	3-OMe
122	S	Me	4-OEt	H	H	H	3-OMe
123	S	Me	4-OEt	H	H	H	3-OAc
124	S	H	2-OEt	7-OEt	H	H	3-OH
125	S	H	2-OEt	7-OEt	H	H	3-OMe
126	S	Me	2-OEt	7-OEt	H	H	3-OMe
127	S	Me	2-OEt	7-OEt	H	H	3-OAc
128	S	H	H	H	H	H	3-OAc
129	S	Me	H	H	H	3-Ac	H
130	S	Ac	H	H	H	3-Ac	3-OAc
131	S	H	7-Ac	H	H	3-Ac	H
132	S	Me	7-Ac	H	H	3-Ac	H
133	S	Ac	7-Ac	H	H	3-Ac	H

Composé	X	R^1	R^2	R^3	R^4	R^5	T
134	S	CH_2OAc	7-Ac	H	H	3-Ac	H
135	S	H	2-Me	4-Cl	H	H	3-OH
136	S	Me	2-Me	4-Cl	H	H	3-OAc
137	S	H	7-Me	2-Me	H	H	3-OH
138	S	Me	7-Me	2-Me	H	H	3-OAc
139	S	H	2-OEt	4-Cl	H	H	3-OH
140	S	Me	2-OEt	4-Cl	H	H	3-OAc
141	S	H	2-S-n-Bu	4-Cl	H	H	3-OH
142	S	Me	2-S-n-Bu	4-Cl	H	H	3-OAc
143	S	Me	4-S-n-Bu	H	H	H	3-OAc
144	S	Me	2-O-Me	4-Br	H	H	3-OAc
145	S	Me	2-O-Me	4-Cl	H	H	3-OAc
146	S	Me	2-O-Me	4-Br	H	H	3-OH
147	S	H	2-O-Me	3-OH	H	H	7-OMe
148	S	H	1-OMe	3-OH	H	H	7-OMe
149	S	H	2-OMe	3-OH	1-Br	H	7-OMe
150	S	H	1-OMe	3-OH	2-Br	H	7-OMe
151	S	H	1-OMe	3-OH	4-Br	H	7-OMe
152	S	H	1-OMe	3-OH	2-Cl	H	7-OMe
153	S	H	1-OMe	3-OH	4-Cl	H	7-OMe
154	S	H	2-OMe	3-OH	1-Cl	H	7-OMe
155	S	H	2-OMe	3-OH	4-Cl	H	7-OMe
156	S	H	2-OEt	3-OH	1-Br	H	7-OEt
157	S	H	2-OEt	3-OH	4-Br	H	7-OEt
158	S	H	2-OEt	3-OH	1-Cl	H	7-OEt
159	S	H	2-OEt	3-OH	4-Cl	H	7-OEt
160	S	H	2-OMe	3-OH	1-Br	7-OMe	9-OMe
161	S	H	2-OMe	3-OH	4-Br	7-OMe	9-OMe

Composé	X	R^1	R^2	R^3	R^4	R^5	Y
162	S	H	2-OMe	3-OH	4-F	H	1-OMe
163	S	H	2-OMe	3-OH	4-CF_3	H	1-OMe
164	S	H	2-OMe	3-OH	4-Br	H	1-OEt
165	S	H	2-OMe	3-OH	4-Cl	H	1-OEt
166	S	H	2-OMe	3-OH	4-F	H	1-OEt
167	S	H	2-OMe	3-OH	4-I	H	1-OMe
168	S	H	2-OMe	3-OH	4-CF_3	H	1-OEt
169	S	H	2-OEt	3-OH	4-Br	H	1-OMe
170	S	H	2-OEt	3-OH	4-Cl	H	1-OMe
171	S	H	2-OEt	3-OH	4-F	H	1-OMe
172	S	H	2-OEt	3-OH	4-CF_3	H	1-OMe
173	S	H	1-OMe	2-OMe	3-OH	4-Br	1-OMe
174	S	H	1-OMe	3-OH	H	H	2-OMe
175	S	H	1-OMe	3-OH	4-Br	H	2-OMe
176	Identique aux composés 147-175 mais X=O						
177	Identique aux composés 147-175 mais X=SO						
178	S	H	2-SMe	3-OH	4-Br	H	1-OMe
179	S	H	2-OMe	3-OH	4-Br	7-SMe	
180	SO_2	H	2-SO_2Me	3-OH	4-Br	H	1-OMe
181	Identique aux composés 147-175 mais X=SO						
182	S	H	4-Cl	H	H	H	3-OBz
183	S	H	4-Cl	H	H	H	3-OCOCH(Me)$_2$
184	S	Ac	H	H	7-F	H	3-OAc
185	S	Me	H	H	7-Me	H	3-OMe
186	S	H	H	H	7-F	H	3-OAc
187	S	Me	H	H	9-Cl	H	3-OMe
188	S	Me	H	H	9-Cl	H	3-OAc
189	S	Me	H	H	7-Me	H	3-OAc

Composé	X	R^1	R^2	R^3	R^4	R^5	T
190	S	H	H	H	9-Cl	H	3-OAc
191	S	H	H	4-CF_3	H	H	3-OAc
192	S	H	H	4-Cl	H	H	3-OTs
193	S	Ac	H	4-Cl	7-F	H	3-OMe
194	S	Ac	H	4-Cl	7-F	H	3-OH
195	S	Me	H	4-Cl	7-F	H	3-OMe
196	SO	H	H	H	H	H	3-OAc
197	SO_2	H	H	H	H	H	3-OAc
198	SO_2	H	H	H	H	H	3-OH
199	SO_2	H	H	H	7-F	H	3-OAc
200	SO_2	H	H	4-Cl	H	H	3-OTs
201	S	H	1-OMe	2-OMe	4-Me	H	3-OH
202	S	H	1-OMe	2-OMe	4-Me	H	3-OAc
203	SO_2	H	1-OMe	2-OMe	4-Me	H	3-OH
204	SO_2	H	4-OMe	H	H	H	3-OH
205	S	H	2-OMe	3-OH	4-Br	7-OMe	H
206	S	H	2-OMe	3-OAc	4-Br	7-OMe	H
207	S	H	2-OMe	3-OAc	4-Cl	7-OMe	H
208	SO_2	H	2-OMe	3-OH	4-Br	7-OMe	H
209	S	H	2-OMe	3-OAc	7-OMe	4-Br	H
210	S	H	2-OMe	3-OAc	7-OMe	4-Br	H
211	S	H	2-OMe	3-OBz	7-OMe	4-Br	H
212	S	Me	2-OMe	3-OMe	7-OMe	4-Br	H
213	S	H	2-OMe	3-OMe	7-OMe	4-Br	H
214	S	Ac	2-OMe	3-OAc	7-OMe	4-Br	H
215	S	Ac	2-OMe	3-OH	7-OMe	4-Br	H
216	S	Ac	2-OMe	3-OMe	7-OMe	4-Br	H
217	S	Me	2-OMe	3-OAc	7-OMe	4-Br	H

Composé	X	R^1	R^2	R^3	R^4	R^5	Y
218	S	Me	2-OMe	3-OH	7-OMe	4-Br	H
219	SO_2	H	2-OMe	3-OH	7-OMe	4-Br	H
220	SO_2	H	2-OMe	3-OAc	7-OMe	4-Br	H
221	SO_2	H	2-OMe	3-OAc	7-OMe	4-Br	H
222	SO	H	2-OMe	3-OAc	7-OMe	4-Br	H
223	SO	H	2-OMe	3-OAc	7-OMe	4-Br	H
224	S	H	2-OMe	$3-OCO_2Me$	4-Br	7-OMe	H
225	S	H	2-OMe	$3-OCO_2Et$	4-Br	7-OMe	H
226	S	H	2-OMe	$3-OCO_2CH(Me)OAc$	4-Br	7-OMe	H
227	S	H	2-OMe	$3-OCO_2CH(Me)OAc$	4-Cl	7-OMe	H
228	S	CO_2Me	2-OMe	3-OH	4-Br	7-OMe	H
229	S	CO_2Et	2-OMe	3-OH	4-Br	7-OMe	H
230	S	$CO_2CH(Ac)OAc$	2-OMe	3-OH	4-Br	7-OMe	H
231	S	$CO_2CH(Me)OAc$	2-OMe	3-OH	4-Cl	7-OMe	H
232	S	$CO_2CH(Me)OAc$	2-OMe	3-OH	4-F	7-OMe	H
233	S	$CO_2CH(Me)OAc$	2-OMe	3-OAc	4-Br	7-OMe	H
234	S	$CO_2CH(Me)OAc$	2-OMe	$3-OCO_2CH(Me)OAc$	4-Br	7-OMe	H
235	O	Ac	2-OMe	3-OH	4-Br	7-OMe	H
236	O	Ac	2-OMe	3-OAc	4-Br	7-OMe	H
237	O	$CO_2CH(Me)OAc$	2-OMe	3-OH	4-Br	7-OMe	H
238	O	$CO_2CH(Me)OAc$	2-OMe	3-OAc	4-Br	7-OMe	H
239	S	H	2-OMe	3-OH	4-Br	7-Me	H
240	S	H	2-OMe	3-OAc	4-Br	7-Me	H
241	S	H	2-OMe	3-OH	4-Br	7-F	H
242	S	H	2-OMe	3-OAc	4-Br	7-F	H

Composé	X	R^1	R^2	R^3	R^4	R^5	T
243	S	H	H	H	H	H	OCOEt
244	S	H	2-Cl	3-Cl	H	H	OCO-n-Pr
245	S	H	H	4-Cl	H	H	OCO-n-Bu
246	S	H	1-Me	H	H	H	H
247	S	H	2-CF_3	H	H	H	H
248	S	H	2-Et	H	H	H	H
249	S	H	H	3-Cl	7-OMe	H	H
250	S	H	H	3-Cl	7-Cl	H	H
251	S	H	H	3-NO_2	H	7-NO_2	H
252	S	H	3-NMe_2	H	H	7-NMe_2	H
253	S	H	1-OH	H	H	H	H
254	S	H	3-OAc	7-F	H	H	H
255	S	H	3-CH_2COMe	4-Cl	H	H	H
256	S	H	3-OCONMe_2	H	4-Cl	H	H
257	S	Ac	3-OMe	4-Cl	H	H	H
258	O	H	2-CF_3	H	H	H	H
259	S	Me	H	3-OMe	H	4-Cl	H
260	SO_2	H	4-Cl	3-OH	H	H	H
261	S	Me	7-F	4-Cl	3-OMe	H	H
262	S	Me	3-OMe	7-Me	H	H	H
263	S	Ac	4-Cl	H	H	H	H
264	S	Ac	3-OAc	4-Cl	H	H	H
265	SO_2	Ac	4-Cl	H	H	H	3-OH
266	SO_2	Ac	4-Cl	H	H	H	3-OAc
267	SO_2	Ac	4-Br	H	H	H	3-OAc

Composé	X	R^1	R^2	R^3	R^4	R^5	I
268	SO_2	$CO_2CH(Me)OAc$	4-Cl	H	H	H	3-OH
269	SO_2	H	4-Cl	H	H	3-$OCO_2CH(Me)OAc$	H
270	O	Ac	4-Cl	H	H	H	3-OAc
271	O	$CO_2CH(Me)OAc$	4-Cl	H	H	H	3-OH
272	O	$CO_2CH(Me)OAc$	4-Cl	H	H	H	3-OAc
273	O	H	4-Cl	H	H	3-$OCO_2CH(Me)OAc$	H
274	S	CH_2OAc	4-Cl	H	H	H	3-OAc
275	S	CH(Me)OAc	4-Cl	H	H	H	3-OAc
276	S	H	2-OMe	3-OH	7-OH	H	H
277	S	H	2-OMe	3-OH	7-OH	4-Br	H
278	S	H	2-OMe	3-OAc	7-OH	4-Br	H
279	S	H	2-OMe	3-OAc	7-OAc	4-Br	H

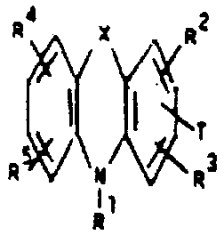
Composé	X	R^1	R^2	R^3	R^4	R^5	I
280	S	Ac	2-OMe	3-OH	7-OH	4-Br	H
281	S	Ac	2-OMe	3-OAc	7-OH	4-Br	H
282	S	Ac	2-OMe	3-OAc	7-OAc	4-Br	H
283	S	Ac	2-OMe	3-OH	7-OAc	4-Br	H
284	SO_2	Ac	2-OMe	3-OH	4-Br	7-OMe	H
285	SO_2	$CO_2CH(Me)OAc$	2-OMe	3-OAc	4-Br	7-OMe	H
286	SO_2	Ac	2-OMe	3-OCO$_2$CH(Me)OAc	4-Br	7-OMe	H
287	SO_2	Ac	2-OMe	3-OAc	4-Br	7-OMe	H
288	SO_2	$CO_2CH(Me)OAc$	2-OMe	3-OH	4-Br	7-OMe	H
289	S	Ac	2-OEt	3-OAc	4-Cl	H	H
290	S	Ac	2-OEt	3-OH	4-Cl	H	H
291	S	Me	H	7-Ac	H	H	3-OMe
292	S	Me	H	H	7-F	H	3-OMe
293	S	Ac	H	H	7-F	H	3-OMe
294	S	Ac	H	H	7-F	H	3-OH

8. Composition selon la revendication 7, dans laquelle le composé répond à l'une des formules numérotées 13, 14, 31, 37, 38, 73, 76, 78, 79, 80, 81, 82, 84, 86, 87, 88, 92, 93, 94, 124, 139, 147, 151, 153, 155, 157, 159, 162, 163, 164, 165, 169, 170, 178, 179, 182 à 223 inclus, 225 à 242 inclus, 260 ou 267 à 294 inclus.

9. Composition selon la revendication 7, dans laquelle le composé répond à l'une des formules numérotées 79, 80, 81, 86, 88, 93, 94, 197, 198, 214, 215, 226, 230, 233, 235, 236, 237, 275, 280, 283, 284, 287, 288, 289 et 290.

10. Composition selon la revendication 1, utilisable pour (a) inhiber la biosynthèse ou l'action de leucotriènes chez les mammifères; (b) traiter les maladies cardiovasculaires; (d) traiter l'inflammation; (d) traiter les allergies; (e) traiter la douleur; (f) traiter l'asthme; ou (g) traiter les troubles de la peau.

11. Composés de formule :



I

dans laquelle les substituants sont tels que définis dans le tableau suivant :

Composé	X	R^1	R^2	R^3	R^4	R^5	T
3	S	Me	4-Cl	H	H	H	3-OMe
8	S	Ac	4-Cl	H	H	H	3-OAc
9	S	Ac	4-Cl	H	H	H	3-OH

Composé	X	R^1	R^2	R^3	R^4	R^5	T
21	S	Ac	H	4-Cl	7-F	H	3-OMe
28	S	Ac	H	4-Cl	7-F	H	3-OH
29	S	Me	H	4-Cl	7-F	H	3-OMe
30	S	H	H	2-OEt	4-Cl	H	3-OH
32	SO_2	H	H	H	H	H	3-OAc
33	SO_2	H	H	4-Cl	H	H	3-OAc
34	SO_2	H	H	4-Cl	H	H	3-OH
39	S	H	1-OMe	2-OMe	4-Me	H	3-OH
40	S	H	1-OMe	2-OMe	4-Me	H	3-OAc
41	SO_2	H	1-OMe	2-OMe	4-Me	H	3-OH

Composé	X	R^1	R^2	R^3	R^4	R^5	I
43	S	H	1-OH	2-C(Me)$_3$	H	4-C(Me)$_3$	H
49	SO	H	1-OMe	2-OMe	4-Me	H	3-OH
50	SO	H	1-OMe	2-OMe	4-Me	H	3-OAc
51	SO_2	H	1-OMe	2-OMe	4-Me	H	3-OAc
52	S	H	2-OMe	3-OH	4-Br	7-OMe	H
53	S	H	2-OMe	3-OH	4-Cl	7-OMe	H
54	S	H	2-OMe	3-OAc	4-Br	7-OMe	H
55	S	H	2-OMe	3-OAc	4-Cl	7-OMe	H
56	SO_2	H	2-OMe	3-OH	4-Br	7-OMe	H
58	SO_2	H	2-OMe	3-OAc	4-Br	7-OMe	H
59	O	Ac	2-OMe	3-OH	4-Br	7-OMe	H
60	O	Ac	2-OMe	3-OAc	4-Br	7-OMe	H
61	O	CO_2CH(Me)OAc	2-OMe	3-OH	4-Br	7-OMe	H
62	O	CO_2CH(Me)OAc	2-OMe	3-OAc	4-Br	7-OMe	H
63	S	H	2-OMe	3-OH	4-Br	7-Me	H
64	S	H	2-OMe	3-OAc	4-Br	7-Me	H
65	S	H	2-OMe	3-OH	4-Br	7-F	H
66	S	H	2-OMe	3-OAc	4-Br	7-F	H
67	SO	H	2-OMe	3-OAc	4-Br	7-OMe	H
68	SO_2	H	2-OMe	3-OH	H	7-OMe	H
69	SO_2	H	2-OMe	3-OAc	H	7-OMe	H
70	S	Ac	2-OMe	4-Br	7-OMe	H	3-OAc

Composé	X	R^1	R^2	R^3	R^4	R^5	I
71	S	Ac	2-OMe	4-Cl	7-OMe	H	3-OAc
72	S	Ac	2-OMe	4-F	7-OMe	H	3-OAc
73	S	Ac	2-OMe	4-I	7-OMe	H	3-OAc
74	S	Ac	2-OMe	4-CF_3	7-OMe	H	3-OAc
75	S	Ac	2-OMe	4-CN	7-OMe	H	3-OAc
76	S	Ac	2-OEt	4-Br	7-OEt	H	3-OAc
77	S	Ac	2-OEt	4-Cl	7-OEt	H	3-OAc
78	S	Ac	2-OMe	4-Br	7-OEt	H	3-OAc
79	S	Ac	2-OMe	4-Cl	7-OEt	H	3-OAc
80	S	Ac	2-OMe	4-F	7-OEt	H	3-OAc
81	S	Ac	2-OEt	4-Br	7-OMe	H	3-OAc
82	S	Ac	2-OEt	4-Cl	7-OMe	H	3-OAc
83	S	Ac	2-OEt	4-F	7-OMe	H	3-OAc
84	S	Ac	2-OEt	4-CF_3	7-OMe	H	3-OAc
85	S	H	2-OMe	4-Br	7-OMe	H	3-OH
86	S	H	2-OMe	4-Cl	7-OMe	H	3-OH
87	S	H	2-OMe	4-F	7-OMe	H	3-OH
88	S	H	2-OMe	4-CF_3	7-OMe	H	3-OH
89	S	H	2-OMe	4-Br	7-OMe	H	3-OAc
90	S	H	2-OMe	4-Br	7-OMe	H	3-OBz
91	S	H	2-OMe	4-Br	7-OMe	H	3-$OCOCHMe_2$
92	S	H	2-OMe	4-Br	7-OMe	3-OCH_2CO_2H	H
93	S	Ac	2-OMe	4-Br	7-OMe	H	3-OBz
94	S	Ac	2-OMe	4-Br	7-OMe	H	3-OMe
95	S	Ac	2-OMe	4-Br	7-OMe	3-OCH_2CO_2H	H
96	S	Ac	2-OMe	4-Cl	7-OMe	3-OCH_2CO_2H	H
97	S	CH_2OAc	2-OMe	4-Br	7-OMe	H	3-OH
98	S	CH_2OAc	2-OMe	4-Cl	7-OMe	H	3-OH
99	S	CH_2OAc	2-OMe	4-Br	7-OMe	H	3-OAc

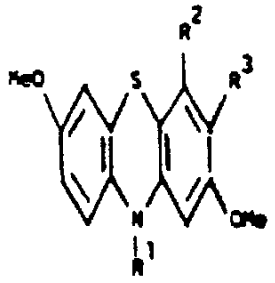
Composé	X	R^1	R^2	R^3	R^4	R^5	I
100	S	CH_2OAc	2-OMe	4-Br	7-OMe	H	3-OBz
101	S	CH_2OAc	2-OMe	4-Br	7-OMe	H	3-OMe
102	S	CH_3	2-OMe	4-Br	7-OMe	H	3-OH
103	S	CH_3	2-OMe	4-Br	7-OMe	H	3-OAc
104	S	CH_3	2-OMe	4-Cl	7-OMe	H	3-OH
105	S	Me	2-OMe	4-F	7-OMe	H	3-OH
106	S	Me	2-OMe	4-CF_3	7-OMe	H	3-OH
107	S	CH(Me)OAc	2-OMe	4-Br	7-OMe	H	3-OH
108	S	$CH(Me)OCOC(Me)_3$	2-OMe	4-Br	7-OMe	H	3-OH
109	S	CH(Me)OAc	2-OMe	4-Cl	7-OMe	H	3-OH
110	S	CH(Me)OAc	2-OMe	4-F	7-OMe	H	3-OH
111	S	CH(Me)OAc	2-OMe	4-CF_3	7-OMe	H	3-OH
112	S	H	2-OMe	4-Br	7-OMe	3-OCO_2Me	H
113	S	H	2-OMe	4-Br	7-OMe	3-OCO_2Et	H
114	S	H	2-OMe	4-Br	7-OMe	3-OCO_2CH(Me)OAc	H
115	S	H	2-OMe	4-Cl	7-OMe	3-OCO_2CH(Me)OAc	H
116	S	CO_2Me	2-OMe	4-Br	7-OMe	H	3-OH
117	S	CO_2Et	2-OMe	4-Br	7-OMe	H	3-OH
118	S	CO_2CH(Me)OAc	2-OMe	4-Br	7-OMe	H	3-OH
119	S	CO_2CH(Me)OAc	2-OMe	4-Cl	7-OMe	H	3-OH
120	S	CO_2CH(Me)OAc	2-OMe	4-F	7-OMe	H	3-OH
121	S	CO_2CH(Me)OAc	2-OMe	4-Br	7-OMe	H	3-OAc
122	S	CO_2CH(Me)OAc	2-OMe	4-Br	7-OMe	3-OCO_2CH(Me)OAc	H
123	S	Ac	2-OMe	4-Br	7-OMe	H	3-OH
124	S	Ac	2-OMe	4-Cl	7-OMe	H	3-OH
125	S	Me	2-OMe	4-Br	7-OMe	H	3-OMe
126	S	H	2-OMe	4-Br	7-OMe	H	3-OMe
127	S	CH(Me)OAc	4-Cl	H	H	H	3-OAc
128	SO_2	Ac	4-Cl	H	H	H	3-OH

Composé	X	R^1	R^2	R^3	R^4	R^5	I
129	SO_2	Ac	4-Cl	H	H	H	3-OAc
130	S	Ac	2-OEt	4-Cl	H	H	3-OH
131	S	Ac	2-OEt	4-Cl	H	H	3-OAc
132	S	Ac	2-OMe	4-Br	7-OH	H	3-OH
133	S	Ac	2-OMe	4-Br	7-OAc	H	3-OH
134	SO_2	Ac	2-OMe	4-Br	7-OMe	H	3-OH
135	SO_2	Ac	2-OMe	4-Br	7-OMe	H	3-OAc
136	SO_2	$CO_2CH(Me)OAc$	2-OMe	4-Br	7-OMe	H	3-OH
137	S	$CO_2\underset{Me}{\underset{\vert}{CH}}OCO\underset{C(Me)_3}{\underset{\vert}{}}$	H	4-Br	7-OMe	2-OMe	3-OH
138	S	H	2-OMe	4-I	7-OMe	H	3-OH
139	S	H	2-OMe	4-CN	7-OMe	H	3-OH
140	S	H	2-OEt	4-Br	7-OEt	H	3-OH
141	S	H	2-OEt	4-Cl	7-OEt	H	3-OH
142	S	H	2-OMe	4-Br	7-OEt	H	3-OH
143	S	H	2-OMe	4-Cl	7-OEt	H	3-OH
144	S	H	2-OMe	4-F	7-OEt	H	3-OH
145	S	H	2-OEt	4-Br	7-OMe	H	3-OH
146	S	H	2-OEt	4-Cl	7-OMe	H	3-OH
147	S	H	2-OEt	4-F	7-OMe	H	3-OH
148	S	H	2-OEt	4-CF_3	7-OMe	H	3-OH

12. Composés dont les variables dans la formule I sont numérotées 3, 8, 9, 32, 33, 34, 41, 59, 60, 61, 70, 71, 114, 118, 119, 121, 123 ou 127 à 137 inclus dans la revendication 11.

13. Composés dont les variables dans la formule I sont numérotées 70, 71, 118, 119, 121, 123 ou 137 dans la revendication 11.

14. Composés selon la revendication 11, de formule :

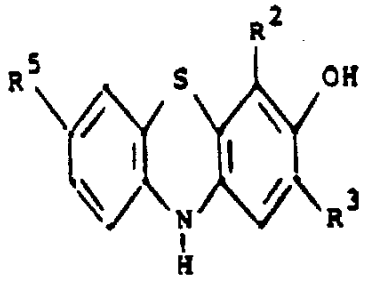


dans laquelle les substituants sont tels que définis dans le tableau suivant :

R^1	R^2	R^3
H	Br	OH
H	Cl	OH
H	F	OH
H	CF_3	OH
H	Br	OAc
H	Br	OCOPh

R^1	R^2	R^3
H	Br	$OCOCHMe_2$
H	Br	OCH_2CO_2H
Ac	Br	OAc
Ac	Cl	OAc
Ac	Br	OCOPh
Ac	Br	OMe
Ac	Br	OCH_2CO_2H
Ac	Cl	OCH_2CO_2H
CH_2OAc	Br	OH
CH_2OAc	Cl	OH
CH_2OAc	Br	OAc
CH_2OAc	Br	OCOPh
CH_2OAc	Br	OMe
CH_3	Br	OH
CH_3	Br	OAc
CH_3	Cl	OH
CH_3	F	OH
CH_3	CF_3	OH
$CH(CH_3)OAc$	Br	OH
$CH(CH_3)OCOC(CH_3)_3$	Br	OH
$CH(CH_3)OAc$	Cl	OH
$CH(CH_3)OAc$	F	OH
$CH(CH_3)OAc$	CF_3	OH
$CO_2CH(Me)OAc$	Br	OH
$CO_2CH(Me)OAc$	Br	OAc

15. Composés selon la revendication 11, de formule :



dans laquelle les substituants sont tels que définis dans le tableau suivant :

R^2	R^3	R^5
Br	OMe	OMe
Cl	OMe	OMe
F	OMe	OMe
I	OMe	OMe
CF_3	OMe	OMe
CN	OMe	OMe
Br	OEt	OEt
Cl	OEt	OEt
Br	OMe	OEt
Cl	OMe	OEt
F	OMe	OEt
Br	OEt	OMe
Cl	OEt	OMe
F	OEt	OMe
CF_3	OEt	OMe

16. 3-Acétoxy-10-acétyl-4-bromo-2,7-diméthoxy-10H-phénothiazine.

17. 10-(1-Acétoxyéthoxycarbonyl)-4-bromo-2,7-diméthoxy-3-hydroxy-10H-phénothiazine.

18. 3-Acétoxy-10-acétyl-4-chloro-2,7-diméthoxy-10H-phénothiazine.

19. 4-Bromo-2,7-diméthoxy-3-hydroxy-10-(1-pivaloyloxyéthoxycarbonyl)-10H-phénothiazine.

20. 3-Hydroxy-10-(1-acétoxyéthoxycarbonyl)-4-chloro-2,7-diméthoxy-10H-phénothiazine.

21. 3-acétoxy-10-(1-acétoxyéthoxycarbonyl)-4-bromo-2,7-diméthoxy-10H-phénothiazine.

22. 3-Hydroxy-10-acétyl-4-bromo-2,7-diméthoxy-10H-phénothiazine.

23. Composition selon l'une quelconque des revendications 1 à 9, comprenant en outre une quantité efficace d'un second ingrédient actif qui est un anti-inflammatoire non stéroïdien; un agent analgésique périphérique; un inhibiteur de cyclooxygénase; un antagoniste de leucotriènes; un inhibiteur de leucotriènes; un antagoniste de récepteurs H_2; un agent antihistaminique; un antagoniste de prostaglandine ou un antagoniste de thromboxane.

24. Composition selon la revendication 23, dans laquelle le rapport pondéral du composé de formule I au second ingrédient actif est dans l'intervalle de 1000:1 à 1:1000.

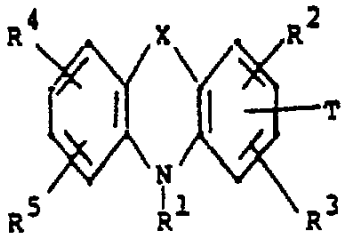
25. Composition selon la revendication 24, dans laquelle ledit rapport est de 200:1 à 1:200.

26. Composition selon l'une quelconque des revendications 23 à 25, dans laquelle le second ingrédient actif est un anti-inflammatoire non stéroïdien.

27. Composition selon la revendication 26, dans laquelle l'anti-inflammatoire non stéroïdien est l'indométhacine.

Ansprüche

1. Pharmazeutische Zusammensetzung, die die Leukotrien-Biosynthese oder -wirkung in Säugetieren inhibieren kann und einen pharmazeutischen Verdünner, Träger oder Exzipienten enthält sowie eine Verbindung der Formel I:



I

worin
X Se, S, SO, SO_2 oder O ist;
R^1 H; C_{1-6}-Alkyl; Acetyl; (C_{1-6}-Acyloxy)-(C_{1-6}-alkyl); Benzoyl; substituiertes Benzoyl mit C_{1-3}-Alkyl, Halogen, CN, CF_3, $COOR^6$, CH_2COOR^6, $(CH_2)_nNR^8R^9$ (worin n 0, 1 oder 2 ist), C_{1-3}-Alkoxy und/oder OH als Substituent (hier als "substituiert wie hier definiert" bezeichnet); Carbamoyl; $CO\text{-}NHR^7$; $COOR^7$; p-Toluolsulfonyl; Methansulfonyl; eine Acylgruppe, so daß R^1-OH eine essentielle Aminosäure ist; Benzyl; Phenethyl; $(CH_2)_pOR^a$, worin R^a C_{1-6}-Alkyl oder Phenyl ist und p eine ganze Zahl von 1 bis 5 ist, wenn R^a Phenyl ist, und eine ganze Zahl von 1 bis 6 ist, wenn R^a Alkyl ist; $(CH_2)_nCOOR^5$, worin n 0, 1 oder 2 ist; oder (C_{1-6}-Acyloxy)-(C_{1-6}-alkoxy)carbonyl ist;
jedes von R^2, R^3, R^4 und R^5 unabhängig von den anderen Wasserstoff; C_{1-6}-Alkyl; C_{2-6}-Alkenyl oder $(CH_2)_qM$ ist, worin q 0 oder eine ganze Zahl von 1 bis 6 ist und H (a) $-OR^{16}$; (b) Halogen; (c) $-CF_3$; (d) $-SR^{16}$; (e) Phenyl oder substituiertes Phenyl, wie hier definiert; (f) $COOR^6$; (g) $-CO\text{-}R^{14}$; (h) Tetrazolyl; (i) $-NH\text{-}CO\text{-}R^7$; (j) $-NR^8R^9$; (k) $-NHSO_2R^{10}$, worin R^{10} OH, C_{1-6}-Alkyl, C_{1-6}-Alkoxy oder Phenyl ist; (l) $-CO\text{-}CH_2OH$; (m) $-SOR^{11}$, worin R^{11} C_{1-6}-Alkyl, Phenyl, substituiertes Phenyl, wie hier definiert, $(CH_2)_mCOOR^6$, worin m eine ganze Zahl von 1 bis 6 ist, CN, Formyl oder C_{1-4}-Perfluoralkyl ist; (n) $-CONR^8R^9$; (o) $-SO_2NR^8R^9$; (P) $-SO_2R^{13}$, worin R^{13} Wasserstoff, OH, C_{1-6}-Alkyl, Phenyl, substituiertes Phenyl, wie hier definiert, $(CH_2)_mCOOR^6$, worin m wie oben definiert ist, CN, Formyl oder C_{1-4}-Perfluoralkyl ist; (q) $-NO_2$; (r) $-O\text{-}CO\text{-}R^{14}$; (S) $O\text{-}CO\text{-}NR^8R^9$; oder (t) -CN ist; jedes R^6, unabhängig von den anderen, Wasserstoff, C_{1-6}-Alkyl oder Phenyl ist;
jedes R^7, unabhängig von den anderen, C_{1-6}-Alkyl, Benzyl, Phenyl oder (C_{1-6}-Acyloxy)-(C_{1-6}-alkyl) ist;
jedes R^8 und jedes R^9, unabhängig von allen anderen, Wasserstoff, C_{1-4}-Acyl, Phenyl oder substituiertes Phenyl, wie hier definiert, ist oder ein R^8 und ein R^9 über das N, an das beide gebunden sind, unter Bildung einer heterocyclischen Gruppe mit 5 bis 8 Ringatomen zusammengenommen sind; jedes R^{14},

unabhängig von den anderen, Wasserstoff, $(CH_2)_rCOOR^6$, worin r 0 oder eine ganze Zahl von 1 bis 4 ist; C_{1-6}-Alkyl; C_{1-6}-Alkoxy; (C_{1-6}-Acyloxy)-(C_{1-6}-alkoxy); Phenyl; substituiertes Phenyl, wie hier definiert; oder C_{1-6}-Aminoalkyl ist, so daß $R^{14}COOH$ eine essentielle Aminosäure ist;
jedes R^{15} unabhängig von allen anderen Wasserstoff, (C_{1-5}-Alkoxy)-(C_{1-5}-alkyl), C_{1-6}-Alkyl; Benzyl; (C_{1-6}-Acyloxy)-(C_{1-6}-alkyl); Phenyl; substituiertes Phenyl, wie hier definiert; $-(CH_2)_mCOOR^6$, worin m wie oben definiert ist; CN; Formyl; Perfluoralkyl; oder CH_2-R^{12} ist, worin R^{12} C_{1-5}-Alkyl, Dimethylamino oder Phenyl ist;
und T Wasserstoff oder $-OR_{15}$ ist, worin R_{15} Wasserstoff, C_{1-6}-Alkyl, (C_{1-6}-Alkyl)acyl, Phenylacyl, substituiertes Phenylacyl, wie hier definiert; Benzoyl, substituiertes Benzoyl, wie hier definiert; oder Arylsulfonyl ist; sowie Verbindungen, die pharmazeutisch annehmbare Salze davon sind.

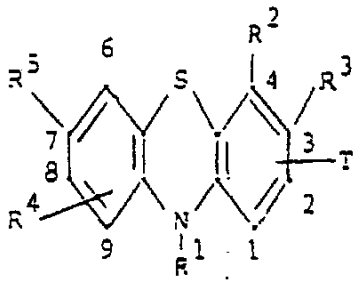
2. Zusammensetzung nach Anspruch 1, worin in der Formel X_1 S, SO, SO_2 oder O ist und die anderen Substituenten wie in Anspruch 1 definiert sind.

3. Zusammensetzung nach Anspruch 2, worin R^2, R^3, R^4 und R^5 alle verschieden von C_{2-6}-Alkenyl sind.

4. Zusammensetzung nach Anspruch 3, worin in der Formel
X S oder O ist;
R^1 H; C_{1-6}-Alkyl; C_{1-6}-Acyl; (C_{1-6}-Acyloxy)-(C_{1-6}-alkyl); (C_{1-6}-Alkoxy)-(C_{1-6}-alkyl); Benzoyl; Benzoyl, substituiert wie hier definiert; Carbamoyl; CO-NHR^7; $COOR^7$; $(CH_2)_pOR^a$, worin R^a C_{1-6}-Alkyl oder Phenyl ist und p eine ganze Zahl von 1 bis 5 ist; $(CH_2)_nCOOR^6$, worin n 0, 1 oder 2 ist; oder (C_{1-6}-Acyloxy)-(C_{1-6}-alkoxy)carbonyl ist;
M, falls in R^2, R^3, R^4 oder R^5 einbezogen, (a) $-OR^{15}$; (b) Halogen; (c) $-CF_3$; (d) $-SR^{15}$; (e) $COOR^6$; (f) -NH-CO-R^7; (g) $-NR^8R^9$; (h) $-SOR^{11}$, worin R^{11} C_{1-6}-Alkyl oder C_{1-4}-Perfluoralkyl ist; (i) $-SO_2R^{13}$, worin R^{13} C_{1-6}-Alkyl oder C_{1-4}-Perfluoralkyl ist; (j) -O-CO-R^{14}, worin R^{14} H, C_{1-6}-Alkyl, Phenyl oder substituiertes Phenyl, wie hier definiert, ist; (k) O-CO-NR^8R^9; oder (1) -CN ist;
jedes R^{15}, unabhängig von den anderen, Wasserstoff; C_{1-6}-Alkyl; Benzyl; (C_{1-6}-Acyloxy)-(C_{1-5}-alkyl) oder C_{1-4}-Perfluoralkyl ist;
T Wasserstoff oder $-OR_{15}$ ist, worin R_{15} Wasserstoff, C_{1-6}-Alkyl, (C_{1-6}-Alkyl)acyl, Phenylacyl, substituiertes Phenylacyl, wie hier definiert, Benzoyl oder substituiertes Benzoyl, wie hier definiert, ist; und die anderen Variablen wie in Anspruch 3 definiert sind.

5. Zusammensetzung nach Anspruch 1, worin in der Formel X O oder S ist;
R^1 Wasserstoff, C_{1-4}-Alkyl, C_{1-4}-Alkylacyl, $-(CH_2)_pOR^a$, worin R^a C_{1-4}-Alkyl oder Phenyl ist und p 1, 2 oder 3 ist, (C_{1-4}-Acyloxy)-(C_{1-4}-alkyl), (C_{1-4}-Alkoxy)carbonyl oder (C_{1-4}-Acyloxy)-(C_{1-4}-alkoxy)-carbonyl ist;
jedes von R^2, R^3, R^4 und R^5 unabhängig von den anderen Wasserstoff, Halogen, Hydroxyl; C_{1-3}-Alkyl; C_{1-3}-Alkoxy; C_{1-3}-Alkylthio; C_{1-5}-Acyloxy; Benzoyloxy; C_{1-3}-Trihalogenalkyl; C_{1-4}-Aminoalkyl; C_{1-5}-Acyl; $(CH_2)_mCOOR^6$, worin m 0, 1, 2, 3 oder 4 ist und R^6 H, Phenyl oder C_{1-6}-Alkyl ist; oder (C_{1-4}-Acyloxy)-(C_{1-4}-alkoxy)carbonyl ist; und
T wie in Anspruch 1 definiert ist.

6. Zusammensetzung nach Anspruch 1, worin die Verbindungen der Formel I durch die Formel III wiedergegeben sind: worin



III

R^1 H, C_{1-4}-Acyl, (C_{1-4}-Acyloxy)-(C_{1-4}-alkyl) oder (C_{1-4}-Acyloxy)-(C_{1-4} -alkoxy)carbonyl ist;
R^2 Halogen ist;
R^3 OH, C_{1-5}-Acyloxy, Benzoyloxy oder (C_{1-4}-Acyloxy)-(C_{1-4}-alkoxy)carbonyloxy ist;
R^4 H, OH, C_{1-4}-Alkoxy oder C_{1-4}-Acyloxy ist und entweder in der Stellung 1 oder der Stellung 2 angeordnet ist;
R^5 OH, C_{1-4}-Alkoxy oder C_{1-4}-Acyloxy ist;
T Wasserstoff oder C_{1-4}-Alkoxy ist;
oder pharmazeutisch annehmbare Salze solcher Verbindungen sind.

7. Zusammensetzung nach Anspruch 1, worin in der Formel die Variablen wie in nachstehender Tabelle angegeben sind:

Verbindung	X	R^1	R^2	R^3	R^4	R^5	T
1	S	H	H	H	H	H	H
2	S	Me	2-t-Bu	4-t-Bu	H	H	1-OH
3	S	Me	2-t-Bu	4-t-Bu	H	H	1-OMe
4	S	Me	2-t-Bu	4-t-Bu	H	H	1-OAc
5	S	Ac	2-t-Bu	4-t-Bu	H	H	1-OH
6	S	H	2-t-Bu	4-t-Bu	H	H	1-OMe
7	S	H	2-t-Bu	4-t-Bu	H	H	1-OAc
8	O	H	2-t-Bu	4-t-Bu	H	H	1-OH
9	S	CH_2OAc	2-t-Bu	4-t-Bu	H	H	1-OH
10	S	H	1-Cl	H	H	H	3-OH
11	S	H	1-Cl	H	H	H	3-OAc
12	S	H	1-Cl	H	H	H	3-OMe
13	S	Me	1-Cl	H	H	H	3-OH
14	S	Me	1-Cl	H	H	H	3-OAc
15	S	Me	1-Cl	H	H	H	3-OMe
16	S	CH_2OAc	1-Cl	H	H	H	3-OMe
17	S	CH_2OAc	1-Cl	H	H	H	3-OAc
18	O	H	1-Cl	H	H	H	3-OH
19	O	Me	1-Cl	H	H	H	3-OH
20	O	Me	1-Cl	H	H	H	3-OAc
21	O	Me	1-Cl	H	H	H	3-OMe

Verbindung	X	R^1	R^2	R^3	R^4	R^5	T
22	O	Ac	1-Cl	H	H	H	3-OAc
23	O	CH_2OAc	1-Cl	H	H	H	3-OMe
24	Se	Me	1-Cl	H	H	H	3-OMe
25	SO	H	1-Cl	H	H	H	3-OH
26	SO	H	1-Cl	H	H	H	3-OMe
27	SO	H	1-Cl	H	H	H	3-OAc
28	SO	Me	1-Cl	H	H	H	3-OH
29	SO	Me	1 Cl	H	H	H	3 OAc
30	SO	Me	1-Cl	H	H	H	3-OMe
31	SO_2	H	1-Cl	H	H	H	3-OH
32	SO_2	H	1-Cl	H	H	H	3-OAc
33	SO_2	H	1-Cl	H	H	H	3-OMe
34	SO_2	Me	1-Cl	H	H	H	3-OAc
35	SO_2	Me	1-Cl	7-OCH_2CO_2H	H	H	3-OAc
36	SO_2	Me	1 Cl	H	H	H	3 OMe
37	SO_2	Ac	1-Cl	H	H	H	3-OH
38	SO_2	Ac	1-Cl	H	H	H	3-OAc
39	SO_2	Ac	1-Cl	H	H	H	3-OMe
40	SO	Ac	1-Cl	H	H	H	3-OH
41	SO	Ac	1-Cl	H	H	H	3-OAc
42	SO	Ac	1 Cl	H	H	H	3-OMe
43	SO_2	CH_2OAc	1-Cl	H	H	H	3-OH
44	SO_2	CH_2OAc	1-Cl	H	H	H	3-OAc
45	SO_2	CH_2OAc	1-Cl	H	H	H	3-OMe
46	S	CH_2Ph	H	H	H	H	H
47	S	Me	H	H	H	H	H

Verbindung	X	R^1	R^2	R^3	R^4	R^5	T
48	S	Ac	H	H	H	H	H
49	S	CH_2OAc	H	H	H	H	H
50	O	H	H	H	H	H	H
51	O	Me	H	H	H	H	H
52	O	Ac	H	H	H	H	H
53	Se	H	H	H	H	H	H
54	Se	Me	H	H	H	H	H
55	Se	Ac	H	H	H	H	H
56	Se	CH_2OAc	H	H	H	H	H
57	SO	H	H	H	H	H	H
58	SO	Me	H	H	H	H	H
59	SO_2	Ac	H	H	H	H	H
60	S	H	H	H	H	H	3-OH
61	S	H	H	H	H	H	3-OAc
62	S	H	H	H	H	H	3-OMe
63	S	Me	H	H	H	H	3-OAc
64	S	Me	H	H	H	H	3-OH
65	S	Me	H	H	H	H	3-OMe
66	S	Ac	H	H	H	H	2-OH
67	S	Ac	H	H	H	H	3-OAc
68	S	Ac	H	H	H	H	3-OMe
69	S	CH_2OAc	H	H	H	H	3-OH
70	S	CH_2OAc	H	H	H	H	3-OAc
71	S	CH_2OAc	H	H	H	H	3-OMe
72	wie Verbindungen 60-71, jedoch X=O						
73	wie Verbindungen 60-71, jedoch X=Se						
74	S	H	4-Cl	H	H	H	3-OH
75	S	H	4-Cl	H	H	H	3-OMe
76	S	H	4-Cl	H	H	H	3-OAc

Verbindung	X	R^1	R^2	R^3	R^4	R^5	T
77	S	Me	4-Cl	H	H	H	3-OH
78	S	Me	4-Cl	H	H	H	3-OAc
79	S	Me	4-Cl	H	H	H	3-OMe
80	S	Ac	4-Cl	H	H	H	3-OH
81	S	Ac	4-Cl	H	H	H	3-OAc
82	S	Ac	4-Cl	H	H	H	3-OMe
83	S	Me	4-Cl	H	H	H	3-O-Bz
84	S	Me	4-Cl	H	H	H	3-OCOCH(Me)$_2$
85	S	Me	4-Cl	H	H	H	3-OCOC(Me)$_3$
86	SO_2	H	4-Cl	H	H	H	3-OH
87	SO_2	H	4-OH	H	H	H	3-OH
88	SO_2	H	4-Cl	H	H	H	3-OAc
89	SO_2	H	4-Cl	H	H	H	3-OMe
90	SO_2	Me	4-Cl	H	H	H	3-OH
91	SO_2	Me	4-Cl	H	H	H	3-OAc
92	SO_2	Me	4-Cl	H	H	H	3-OMe
93	SO_2	Ac	4-Cl	H	H	H	3-OH
94	SO_2	Ac	4-Cl	H	H	H	3-OAc
95	SO_2	Ac	4 Cl	H	H	H	3-OMe
96	S	CH_2OAc	4 Cl	H	H	H	H
97	S	CH_2OAc	4-Cl	H	H	H	3-OH
98	S	CH_2OAc	4-Cl	H	H	H	3-OAc
99	S	CH_2OAc	4-Cl	H	H	H	3-OMe
100	SO_2	CH_2OAc	4-Cl	H	H	H	3 OH
101	SO_2	CH_2OAc	4-Cl	H	H	H	3-OAc
102	SO_2	CH_2CAc	4-Cl	H	H	H	3-OMe
103	wie Verbindungen 74-103, jedoch X=SO						
104	wie Verbindungen 74-103, jedoch X=O						
105	wie Verbindungen 74-103, jedoch ist R_4 7-Cl						

Verbindung	X	R^1	R^2	R^3	R^4	R^5	T
106	wie Verbindung 105, jedoch X=O						
107	wie Verbindungen 74-103, jedoch ist R_4 7-OMe						
108	wie Verbindung 107, jedoch X=O						
109	wie Verbindungen 74-103, jedoch ist R_4 7-C_{1-6}-Alkyl						
110	wie Verbindung 109, jedoch X=O						
111	wie Verbindunge 74-103, jedoch ist R_4 7-COMe						
112	wie Verbindung 111, jedoch X=O						
113	wie Verbindungen 74-103, jedoch ist R_4 7-$CH_{2m}COOR$, worin m 0 bis 4 ist						
114	wie Verbindung 113, jedoch X=O						
115	wie Verbindungen 74-103, jedoch ist R_4 9-Cl						
116	S	H	4-Et	H	H	H	3-OH
117	S	Me	4-Et	H	H	H	3-$OCOCH_2Ph$
118	S	Me	4-Et	H	H	H	3-OAc
119	S	Me	4-Et	H	H	H	3-OMe
120	S	H	4-OEt	H	H	H	3-OH
121	S	H	4-OEt	H	H	H	3-OMe
122	S	Me	4-OEt	H	H	H	3-OMe
123	S	Me	4-OEt	H	H	H	3-OAc
124	S	H	2-OEt	7-OEt	H	H	3-OH
125	S	H	2-OEt	7-OEt	H	H	3-OMe
126	S	Me	2-OEt	7-OEt	H	H	3-OMe
127	S	Me	2-OEt	7-OEt	H	H	3-OAc
128	S	H	H	H	H	H	3-OAc
129	S	Me	H	H	H	3-Ac	H
130	S	Ac	H	H	H	3-Ac	3-OAc
131	S	H	7-Ac	H	H	3-Ac	H
132	S	Me	7-Ac	H	H	3-Ac	H
133	S	Ac	7-Ac	H	H	3-Ac	H

Verbindung	X	R^1	R^2	R^3	R^4	R^5	T
134	S	CH_2OAc	7-Ac	H	H	3-Ac	H
135	S	H	2-Me	4-Cl	H	H	3-OH
136	S	Me	2-Me	4-Cl	H	H	3-OAc
137	S	H	7-Me	2-Me	H	H	3-OH
138	S	Me	7-Me	2-Me	H	H	3-OAc
139	S	H	2-OEt	4-Cl	H	H	3-OH
140	S	Me	2-OEt	4-Cl	H	H	3-OAc
141	S	H	2-S-n-Bu	4-Cl	H	H	3-OH
142	S	Me	2-S-n-Bu	4-Cl	H	H	3-OAc
143	S	Me	4-S-n-Bu	H	H	H	3-OAc
144	S	Me	2-O-Me	4-Br	H	H	3-OAc
145	S	Me	2-O-Me	4-Cl	H	H	3-OAc
146	S	Me	2-O-Me	4-Br	H	H	3-OH
147	S	H	2-O-Me	3-OH	H	H	7-OMe
148	S	H	1-OMe	3-OH	H	H	7-OMe
149	S	H	2-OMe	3-OH	1-Br	H	7-OMe
150	S	H	1-OMe	3-OH	2-Br	H	7-OMe
151	S	H	1-OMe	3-OH	4-Br	H	7-OMe
152	S	H	1-OMe	3-OH	2-Cl	H	7-OMe
153	S	H	1-OMe	3-OH	4-Cl	H	7-OMe
154	S	H	2-OMe	3-OH	1-Cl	H	7-OMe
155	S	H	2-OMe	3-OH	4-Cl	H	7-OMe
156	S	H	2-OEt	3-OH	1-Br	H	7-OEt
157	S	H	2-OEt	3-OH	4-Br	H	7-OEt
158	S	H	2-OEt	3-OH	1-Cl	H	7-OEt
159	S	H	2-OEt	3-OH	4-Cl	H	7-OEt
160	S	H	2-OMe	3-OH	1-Br	7-OMe	9-OMe
161	S	H	2-OMe	3-OH	4-Br	7-OMe	8-OMe

Verbindung	X	R^1	R^2	R^3	R^4	R^5	T
162	S	H	2-OMe	3-OH	4-F	H	7-OMe
163	S	H	2-OMe	3-OH	4-CF_3	H	7-OMe
164	S	H	2-OMe	3-OH	4-Br	H	7-OEt
165	S	H	2-OMe	3-OH	4-Cl	H	7-OEt
166	S	H	2-OMe	3-OH	4-F	H	7-OEt
167	S	H	2-OMe	3-OH	4-I	H	7-OMe
168	S	H	2-OMe	3-OH	4-CF_3	H	7-OEt
169	S	H	2-OEt	3-OH	4-Br	H	7-OMe
170	S	H	2-OEt	3-OH	4-Cl	H	7-OMe
171	S	H	2-OEt	3-OH	4-F	H	7-OMe
172	S	H	2-OEt	3-OH	4-CF_3	H	7-OMe
173	S	H	1-OMe	2-OMe	3-OH	4-Br	7-OMe
174	S	H	1-OMe	3-OH	H	H	2-OMe
175	S	H	1-OMe	3-OH	4-Br	H	2-OMe
176	wie Verbindungen 147-175, jedoch X=O						
177	wie Verbindungen 147-175, jedoch X=SO_2						
178	S	H	2-SMe	3-OH	4-Br	H	7-OMe
179	S	H	2-OMe	3-OH	4-Br	7-SMe	
180	SO_2	H	2-SO_2Me	3-OH	4-Br	H	7-OMe
181	wie Verbindungen 147-175, jedoch X=SO						
182	S	H	4-Cl	H	H	H	3-OBz
183	S	H	4-Cl	H	H	H	3-OCOCH(Me)$_2$
184	S	Ac	H	H	7-F	H	3-OAc
185	S	Me	H	H	7-Me	H	3-OMe
186	S	H	H	H	7-F	H	3-OAc
187	S	Me	H	H	9-Cl	H	3-OMe
188	S	Me	H	H	9-Cl	H	3-OAc
189	S	Me	H	H	7-Me	H	3-OAc

Verbindung	X	R^1	R^2	R^3	R^4	R^5	T
190	S	H	H	H	9-Cl	H	3-OAc
191	S	H	H	4-CF_3	H	H	3 OAc
192	S	H	H	4-Cl	H	H	3-OTs
193	S	Ac	H	4-Cl	7-F	H	3-OMe
194	S	Ac	H	4-Cl	7-F	H	3-OH
195	S	Me	H	4-Cl	7-F	H	3-OMe
196	SO	H	H	H	H	H	3 OAc
197	SO_2	H	H	H	H	H	3 OAc
198	SO_2	H	H	H	H	H	3 OH
199	SO_2	H	H	H	7-F	H	3-OAc
200	SO_2	H	H	4-Cl	H	H	3-OTs
201	S	H	1-OMe	2-OMe	4-Me	H	3-OH
202	S	H	1-OMe	2-OMe	4-Me	H	3-OAc
203	SO_2	H	1-OMe	2-OMe	4-Me	H	3-OH
204	SO_2	H	4-OMe	H	H	H	3 OH
205	S	H	2-OMe	3-OH	4-Br	7-OMe	H
206	S	H	2-OMe	3-OAc	4-Br	7-OMe	H
207	S	H	2-OMe	3-OAc	4-Cl	7-OMe	H
208	SO_2	H	2-OMe	3-OH	4-Br	7-OMe	H
209	S	H	2-OMe	3-OAc	7-OMe	4-Br	H
210	S	H	2-OMe	3-OAc	7-OMe	4-Br	H
211	S	H	2-OMe	3-OBz	7-OMe	4-Br	H
212	S	Me	2-OMe	3-OMe	7-OMe	4-Br	H
213	S	H	2-OMe	3-OMe	7-OMe	4-Br	H
214	S	Ac	2-OMe	3-OAc	7-OMe	4-Br	H
215	S	Ac	2-OMe	3-OH	7-OMe	4-Br	H
216	S	Ac	2-OMe	3-OMe	7-OMe	4-Br	H
217	S	Me	2-OMe	3-OAc	7-OMe	4-Br	H

Verbindung	X	R^1	R^2	R^3	R^4	R^5	T
218	S	Me	2-OMe	3-OH	7-OMe	4-Br	H
219	SO_2	H	2-OMe	3-OH	7-OMe	4-Br	H
220	SO_2	H	2-OMe	3-OAc	7-OMe	4-Br	H
221	SO_2	H	2-OMe	3-OAc	7-OMe	4-Br	H
222	SO	H	2-OMe	3-OAc	7-OMe	4-Br	H
223	SO	H	2-OMe	3-OAc	7-OMe	4-Br	H
224	S	H	2-OMe	$3-OCO_2Me$	4-Br	7-OMe	H
225	S	H	2-OMe	$3-OCO_2Et$	4-Br	7-OMe	H
226	S	H	2-OMe	$3-OCO_2CH(Me)OAc$	4-Br	7-OMe	H
227	S	H	2-OMe	$3-OCO_2CH(Me)OAc$	4-Cl	7-OMe	H
228	S	CO_2Me	2-OMe	3-OH	4-Br	7-OMe	H
229	S	CO_2Et	2-OMe	3-OH	4-Br	7-OMe	H
230	S	$CO_2CH(Me)OAc$	2-OMe	3-OH	4-Br	7-OMe	H
231	S	$CO_2CH(Me)OAc$	2-OMe	3-OH	4-Cl	7-OMe	H
232	S	$CO_2CH(Me)OAc$	2-OMe	3-OH	4-F	7-OMe	H
233	S	$CO_2CH(Me)OAc$	2-OMe	3-OAc	4-Br	7-OMe	H
234	S	$CO_2CH(Me)OAc$	2-OMe	$3-OCO_2CH(Me)OAc$	4-Br	7-OMe	H
235	O	Ac	2-OMe	3-OH	4-Br	7-OMe	H
236	O	Ac	2-OMe	3-OAc	4-Br	7-OMe	H
237	O	$CO_2CH(Me)OAc$	2-OMe	3-OH	4-Br	7-OMe	H
238	O	$CO_2CH(Me)OAc$	2-OMe	3-OAc	4-Br	7-OMe	H
239	S	H	2-OMe	3-OH	4-Br	7-Me	H
240	S	H	2-OMe	3-OAc	4-Br	7-Me	H
241	S	H	2-OMe	3-OH	4-Br	7-F	H
242	S	H	2-OMe	3-OAc	4-Br	7-F	H

Verbindung	X	R^1	R^2	R^3	R^4	R^5	I
243	S	H	H	H	H	H	OCOEt
244	S	H	2-Cl	3-Cl	H	H	OCO-n-Pr
245	S	H	H	4-Cl	H	H	OCO-n-Bu
246	S	H	1-Me	H	H	H	H
247	S	H	2-CF_3	H	H	H	H
248	S	H	2-Et	H	H	H	H
249	S	H	H	3-Cl	7-OMe	H	H
250	S	H	H	3-Cl	7-Cl	H	H
251	S	H	H	3-NO_2	H	7-NO_2	H
252	S	H	3-NMe_2	H	H	7-NMe_2	H
253	S	H	1-OH	H	H	H	H
254	S	H	3-OAc	7-F	H	H	H
255	S	H	3-CH_2COMe	4-Cl	H	H	H
256	S	H	3-$OCOCHMe_2$	H	4-Cl	H	H
257	S	Ac	3-OMe	4-Cl	H	H	H
258	O	H	2-CF_3	H	H	H	H
259	S	Me	H	3-OMe	H	4-Cl	H
260	SO_2	H	4-Cl	3-OH	H	H	H
261	S	Me	7-F	4-Cl	3-OMe	H	H
262	S	Me	3-OMe	7-Me	H	H	H
263	S	Ac	4-Cl	H	H	H	H
264	S	Ac	3-OAc	4-Cl	H	H	H
265	SO_2	Ac	4-Cl	H	H	H	3-OH
266	SO_2	Ac	4-Cl	H	H	H	3-OAc
267	SO_2	Ac	4-Br	H	H	H	3-OAc

Verbindung	X	R^1	R^2	R^3	R^4	R^5	I
268	SO_2	$CO_2CH(Me)OAc$	4-Cl	H	H	H	3-OH
269	SO_2	H	4-Cl	H	H	3-$OCO_2CH(Me)OAc$	H
270	O	Ac	4-Cl	H	H	H	3-OAc
271	O	$CO_2CH(Me)OAc$	4-Cl	H	H	H	3-OH
272	O	$CO_2CH(Me)OAc$	4-Cl	H	H	H	2-OAc
273	O	H	4-Cl	H	H	3-$OCO_2CH(Me)OAc$	H
274	S	CH_2OAc	4-Cl	H	H	H	3-OAc
275	S	CH(Me)OAc	4-Cl	H	H	H	3-OAc
276	S	H	2-OMe	3-OH	7-OH	H	H
277	S	H	2-OMe	3-OH	7-OH	4-Br	H
278	S	H	2-OMe	3-OAc	7-OH	4-Br	H
279	S	H	2-OMe	3-OAc	7-OAc	4-Br	H

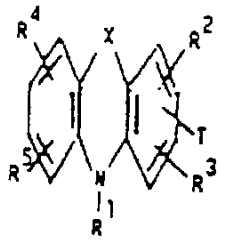
Verbindung	X	R^1	R^2	R^3	R^4	R^5	I
280	S	Ac	2-OMe	3-OH	7-OH	4-Br	H
281	S	Ac	2-OMe	3-OAc	7-OH	4-Br	H
282	S	Ac	2-OMe	3-OAc	7-OAc	4-Br	H
283	S	Ac	2-OMe	3-OH	7-OAc	4-Br	H
284	SO_2	Ac	2-OMe	3-OH	4-Br	7-OMe	H
285	SO_2	$CO_2CH(Me)OAc$	2-OMe	3-OAc	4-Br	7-OMe	H
286	SO_2	Ac	2-OMe	3-OCO$_2$CH(Me)OAc	4-Br	7-OMe	H
287	SO_2	Ac	2-OMe	3-OAc	4-Br	7-OMe	H
288	SO_2	$CO_2CH(Me)OAc$	2-OMe	3-OH	4-Br	7-OMe	H
289	S	Ac	2-OEt	3-OAc	4-Cl	H	H
290	S	Ac	2-OEt	3-OH	4-Cl	H	H
291	S	Me	H	7-Ac	H	H	3-OMe
292	S	Me	H	H	7-F	H	3-OMe
293	S	Ac	H	H	7-F	H	3-OMe
294	S	Ac	H	H	7-F	H	3-OH

8. Zusammensetzung nach Anspruch 7, worin die Verbindung eine der mit 13, 14, 31, 37, 38, 73, 76, 78, 79, 80, 81, 82, 84, 86, 87, 88, 92, 93, 94, 124, 139, 147, 151, 153, 155, 157, 159, 162, 163, 164, 165, 169, 170, 178, 179, 182 bis 223 einschließlich, 225 bis 242 einschließlich, 260 oder 267 bis 294 einschließlich numerierten Formeln hat.

9. Zusammensetzung nach Anspruch 7, worin die Verbindung eine der mit 79, 80, 81, 86, 88, 93, 94, 197, 198, 214, 215, 226, 230, 233, 235, 236, 237, 275, 280, 283, 284, 287, 288, 289 und 290 numerierten Formeln hat.

10. Zusammensetzung nach Anspruch 1 zur Verwendung bei der (a) Inhibierung der Leukotrien-Biosynthese oder -wirkung in Säugetieren; (b) Behandlung von Herz-Kreislauf-Zuständen; (c) Behandlung von Entzündungen; (d) Behandlung von Allergien; (e) Behandlung von Schmerz; (f) Behandlung von Asthma; oder (g) Behandlung von Hautzuständen.

11. Verbindungen der Formel:



I

worin die Substituenten wie in der nachstehenden Tabelle angegeben sind:

Verbindung	X	R^1	R^2	R^3	R^4	R^5	T
3	S	Me	4-Cl	H	H	H	3-OMe
8	S	Ac	4-Cl	H	H	H	3-OAc
9	S	Ac	4-Cl	H	H	H	3-OH

Verbindung	X	R^1	R^2	R^3	R^4	R^5	T
27	S	Ac	H	4-Cl	7-F	H	3-OMe
28	S	Ac	H	4-Cl	7-F	H	3-OH
29	S	Me	H	4-Cl	7-F	H	3-OMe
30	S	H	H	2-OEt	4-Cl	H	3-OH
32	SO_2	H	H	H	H	H	3-OAc
33	SO_2	H	H	4-Cl	H	H	3-OAc
34	SO_2	H	H	4-Cl	H	H	3-OH
39	S	H	1-OMe	2-OMe	4-Me	H	3-OH
40	S	H	1-OMe	2-OMe	4-Me	H	3-OAc
41	SO_2	H	1-OMe	2-OMe	4-Me	H	3-OH

Verbindung	X	R^1	R^2	R^3	R^4	R^5	I
43	S	H	1-OH	2-$C(Me)_3$	H	4-$C(Me)_3$	H
49	SO	H	1-OMe	2-OMe	4-Me	H	3-OH
50	SO	H	1-OMe	2-OMe	4-Me	H	3-OAc
51	SO_2	H	1-OMe	2-OMe	4-Me	H	3-OAc
52	S	H	2-OMe	3-OH	4-Br	7-OMe	H
53	S	H	2-OMe	3-OH	4-Cl	7-OMe	H
54	S	H	2-OMe	3-OAc	4-Br	7-OMe	H
55	S	H	2-OMe	3-OAc	4-Cl	7-OMe	H
56	SO_2	H	2-OMe	3-OH	4-Br	7-OMe	H
58	SO_2	H	2-OMe	3-OAc	4-Br	7-OMe	H
59	O	Ac	2-OMe	3-OH	4-Br	7-OMe	H
60	O	Ac	2-OMe	3-OAc	4-Br	7-OMe	H
61	O	$CO_2CH(Me)OAc$	2-OMe	3-OH	4-Br	7-OMe	H
62	O	$CO_2CH(Me)OAc$	2-OMe	3-OAc	4-Br	7-OMe	H
63	S	H	2-OMe	3-OH	4-Br	7-Me	H
64	S	H	2-OMe	3-OAc	4-Br	7-Me	H
65	S	H	2-OMe	3-OH	4-Br	7-F	H
66	S	H	2-OMe	3-OAc	4-Br	7-F	H
67	SO	H	2-OMe	3-OAc	4-Br	7-OMe	H
68	SO_2	H	2-OMe	3-OH	H	7-OMe	H
69	SO_2	H	2-OMe	3-OAc	H	7-OMe	H
70	S	Ac	2-OMe	4-Br	7-OMe	H	3-OAc

Verbindung	X	R^1	R^2	R^3	R^4	R^5	I
71	S	Ac	2-OMe	4-Cl	7-OMe	H	3-OAc
72	S	Ac	2-OMe	4-F	7-OMe	H	3-OAc
73	S	Ac	2-OMe	4-I	7-OMe	H	3-OAc
74	S	Ac	2-OMe	4-CF_3	7-OMe	H	3-OAc
75	S	Ac	2-OMe	4-CN	7-OMe	H	3-OAc
76	S	Ac	2-OEt	4-Br	7-OEt	H	3-OAc
77	S	Ac	2-OEt	4-Cl	7-OEt	H	3-OAc
78	S	Ac	2-OMe	4-Br	7-OEt	H	3-OAc
79	S	Ac	2-OMe	4-Cl	7-OEt	H	3-OAc
80	S	Ac	2-OMe	4-F	7-OEt	H	3-OAc
81	S	Ac	2-OEt	4-Br	7-OMe	H	3-OAc
82	S	Ac	2-OEt	4-Cl	7-OMe	H	3-OAc
83	S	Ac	2-OEt	4-F	7-OMe	H	3-OAc
84	S	Ac	2-OEt	4-CF_3	7-OMe	H	3-OAc
85	S	H	2-OMe	4-Br	7-OMe	H	3-OH
86	S	H	2-OMe	4-Cl	7-OMe	H	3-OH
87	S	H	2-OMe	4-F	7-OMe	H	3-OH
88	S	H	2-OMe	4-CF_3	7-OMe	H	3-OH
89	S	H	2-OMe	4-Br	7-OMe	H	3-OAc
90	S	H	2-OMe	4-Br	7-OMe	H	3-OBz
91	S	H	2-OMe	4-Br	7-OMe	H	3-OCOCHMe$_2$
92	S	H	2-OMe	4-Br	7-OMe	3-OCH_2CO_2H	H
93	S	Ac	2-OMe	4-Br	7-OMe	H	3-OBz
94	S	Ac	2-OMe	4-Br	7-OMe	H	3-OMe
95	S	Ac	2-OMe	4-Br	7-OMe	3-OCH_2CO_2H	H
96	S	Ac	2-OMe	4-Cl	7-OMe	3-OCH_2CO_2H	H
97	S	CH_2OAc	2-OMe	4-Br	7-OMe	H	3-OH
98	S	CH_2OAc	2-OMe	4-Cl	7-OMe	H	3-OH
99	S	CH_2OAc	2-OMe	4-Br	7-OMe	H	3-OAc

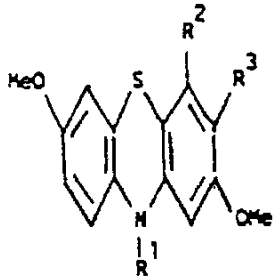
Verbindung	X	R^1	R^2	R^3	R^4	R^5	I
100	S	CH_2OAc	2-OMe	4-Br	7-OMe	H	3-OBz
101	S	CH_2OAc	2-OMe	4-Br	7-OMe	H	3-OMe
102	S	CH_3	2-OMe	4-Br	7-OMe	H	3-OH
103	S	CH_3	2-OMe	4-Br	7-OMe	H	3-OAc
104	S	CH_3	2-OMe	4-Cl	7-OMe	H	3-OH
105	S	Me	2-OMe	4-F	7-OMe	H	3-OH
106	S	Me	2-OMe	$4-CF_3$	7-OMe	H	3-OH
107	S	CH(Me)OAc	2-OMe	4-Br	7-OMe	H	3-OH
108	S	$CH(Me)OCOC(Me)_3$	2-OMe	4-Br	7-OMe	H	3-OH
109	S	CH(Me)OAc	2-OMe	4-Cl	7-OMe	H	3-OH
110	S	CH(Me)OAc	2-OMe	4-F	7-OMe	H	3-OH
111	S	CH(Me)OAc	2-OMe	$4-CF_3$	7-OMe	H	3-OH
112	S	H	2-OMe	4-Br	7-OMe	$3-OCO_2Me$	H
113	S	H	2-OMe	4-Br	7-OMe	$3-OCO_2Et$	H
114	S	H	2-OMe	4-Br	7-OMe	$3-OCO_2CH(Me)OAc$	H
115	S	H	2-OMe	4-Cl	7-OMe	$3-OCO_2CH(Me)OAc$	H
116	S	CO_2Me	2-OMe	4-Br	7-OMe	H	3-OH
117	S	CO_2Et	2-OMe	4-Br	7-OMe	H	3-OH
118	S	$CO_2CH(Me)OAc$	2-OMe	4-Br	7-OMe	H	3-OH
119	S	$CO_2CH(Me)OAc$	2-OMe	4-Cl	7-OMe	H	3-OH
120	S	$CO_2CH(Me)OAc$	2-OMe	4-F	7-OMe	H	3-OH
121	S	$CO_2CH(Me)OAc$	2-OMe	4-Br	7-OMe	H	3-OAc
122	S	$CO_2CH(Me)OAc$	2-OMe	4-Br	7-OMe	$3-OCO_2CH(Me)OAc$	H
123	S	Ac	2-OMe	4-Br	7-OMe	H	3-OH
124	S	Ac	2-OMe	4-Cl	7-OMe	H	3-OH
125	S	Me	2-OMe	4-Br	7-OMe	H	3-OMe
126	S	H	2-OMe	4-Br	7-OMe	H	3-OMe
127	S	CH(Me)OAc	4-Cl	H	H	H	3-OAc
128	SO_2	Ac	4-Cl	H	H	H	3-OH

Verbindung	X	R^1	R^2	R^3	R^4	R^5	I
129	SO_2	Ac	4-Cl	H	H	H	3-OAc
130	S	Ac	2-OEt	4-Cl	H	H	3-OH
131	S	Ac	2-OEt	4-Cl	H	H	3-OAc
132	S	Ac	2-OMe	4-Br	7-OH	H	3-OH
133	S	Ac	2-OMe	4-Br	7-OAc	H	3-OH
134	SO_2	Ac	2-OMe	4-Br	7-OMe	H	3-OH
135	SO_2	Ac	2-OMe	4-Br	7-OMe	H	3-OAc
136	SO_2	$CO_2CH(Me)OAc$	2-OMe	4-Br	7-OMe	H	3-OH
137	S	CO_2CHOCO (Me; $C(Me)_3$)	H	4-Br	7-OMe	2-OMe	3-OH
138	S	H	2-OMe	4-I	7-OMe	H	3-OH
139	S	H	2-OMe	4-CN	7-OMe	H	3-OH
140	S	H	2-OEt	4-Br	7-OEt	H	3-OH
141	S	H	2-OEt	4-Cl	7-OEt	H	3-OH
142	S	H	2-OMe	4-Br	7-OEt	H	3-OH
143	S	H	2-OMe	4-Cl	7-OEt	H	3-OH
144	S	H	2-OMe	4-F	7-OEt	H	3-OH
145	S	H	2-OEt	4-Br	7-OMe	H	3-OH
146	S	H	2-OEt	4-Cl	7-OMe	H	3-OH
147	S	H	2-OEt	4-F	7-OMe	H	3-OH
148	S	H	2-OEt	4-CF_3	7-OMe	H	3-OH

12. Verbindungen mit Variablen in Formel I, in Anspruch 11 mit 3, 8, 9, 32, 33, 34, 41, 59, 60, 61, 70, 71, 114, 118, 119, 121, 123 oder 127 bis 137 einschließlich numeriert.

13. Verbindungen mit Variablen in Formel I, in Anspruch 11 mit 70, 71, 118, 119, 121, 123 oder 137 numeriert.

14. Verbindungen nach Anspruch 11 mit der Formel:

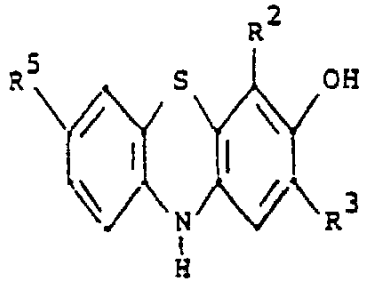


worin die Substituenten wie in der nachstehenden Tabelle angegeben sind:

R^1	R^2	R^3
H	Br	OH
H	Cl	OH
H	F	OH
H	CF_3	OH
H	Br	OAc
H	Br	OCOPh

R^1	R^2	R^3
H	Br	$OCOCHMe_2$
H	Br	OCH_2CO_2H
Ac	Br	OAc
Ac	Cl	OAc
Ac	Br	OCOPh
Ac	Br	OMe
Ac	Br	OCH_2CO_2H
Ac	Cl	OCH_2CO_2H
CH_2OAc	Br	OH
CH_2OAc	Cl	OH
CH_2OAc	Br	OAc
CH_2OAc	Br	OCOPh
CH_2OAc	Br	OMe
CH_3	Br	OH
CH_3	Br	OAc
CH_3	Cl	OH
CH_3	F	OH
CH_3	CF_3	OH
$CH(CH_3)OAc$	Br	OH
$CH(CH_3)OCOC(CH_3)_3$	Br	OH
$CH(CH_3)OAc$	Cl	OH
$CH(CH_3)OAc$	F	OH
$CH(CH_3)OAc$	CF_3	OH
$CO_2CH(Me)OAc$	Br	OH
$CO_2CH(Me)OAc$	Br	OAc

15. Verbindungen nach Anspruch 11 der Formel



worin die Substituenten wie in der nachstehenden Tabelle angegeben sind:

R^2	R^3	R^5
Br	OMe	OMe
Cl	OMe	OMe
F	OMe	OMe
I	OMe	OMe
CF_3	OMe	OMe
CN	OMe	OMe
Br	OEt	OEt
Cl	OEt	OEt
Br	OMe	OEt
Cl	OMe	OEt
F	OMe	OEt
Br	OEt	OMe
Cl	OEt	OMe
F	OEt	OMe
CF_3	OEt	OMe

16. 3-Acetoxy-10-acetyl-4-brom-2,7-dimethoxy-10H-phenothiazin.

17. 10-(1-Acetoxyethoxycarbonyl)-4-brom-2,7-dimethoxy-3-hydroxy-10H-phenothiazin.

18. 3-Acetoxy-10-acetyl-4-chlor-2,7-dimethoxy-10H-phenothiazin.

19. 4-Brom-2,7-dimethoxy-3-hydroxy-10-(1-pivaloyloxyethoxycarbonyl)-10H-phenothiazin.

20. 3-Hydroxy-10-(1-acetoxyethoxycarbonyl)-4-chlor-2,7-dimethoxy-10H-phenothiazin.

21. 3-Acetoxy-10-(1-acetoxyethoxycarbonyl)-4-brom-2,7-dimethoxy-10H-phenothiazin.

22. 3-Hydroxy-10-acetyl-4-brom-2,7-dimethoxy-10H-phenothiazin.

23. Zusammensetzung nach einem der Ansprüche 1 bis 9, welche zusätzlich eine wirksame Menge eines zweiten wirksamen Bestandteils umfaßt, der ein nicht steroides entzündungshemmendes Mittel; ein peripheres Analgetikum; ein Cyclooxygenaseinhibitor; ein Leukotrienantagonist; ein Leukotrieninhibitor; ein H_2-Rezeptor-Antagonist; ein Antihistaminikum; ein Prostaglandinantagonist oder ein Thromboxanantagonist ist.

24. Zusammensetzung nach Anspruch 23, worin das Gewichtsverhältnis der Verbindung der Formel I zum zweiten wirksamen Bestandteil im Bereich von 1000:1 bis 1:1000 liegt.

25. Zusammensetzung nach Anspruch 24, worin das Verhältnis 200:1 bis 1:200 ist.

26. Zusammensetzung nach einem der Ansprüche 23 bis 25, worin der zweite wirksame Bestandteil ein nicht steroides entzündungshemmendes Mittel ist.

27. Zusammensetzung nach Anspruch 26, worin das nicht steroide entzündungshemmende Mittel Indomethazin ist.